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Vol. 17 MARCH, 1945 No. 3

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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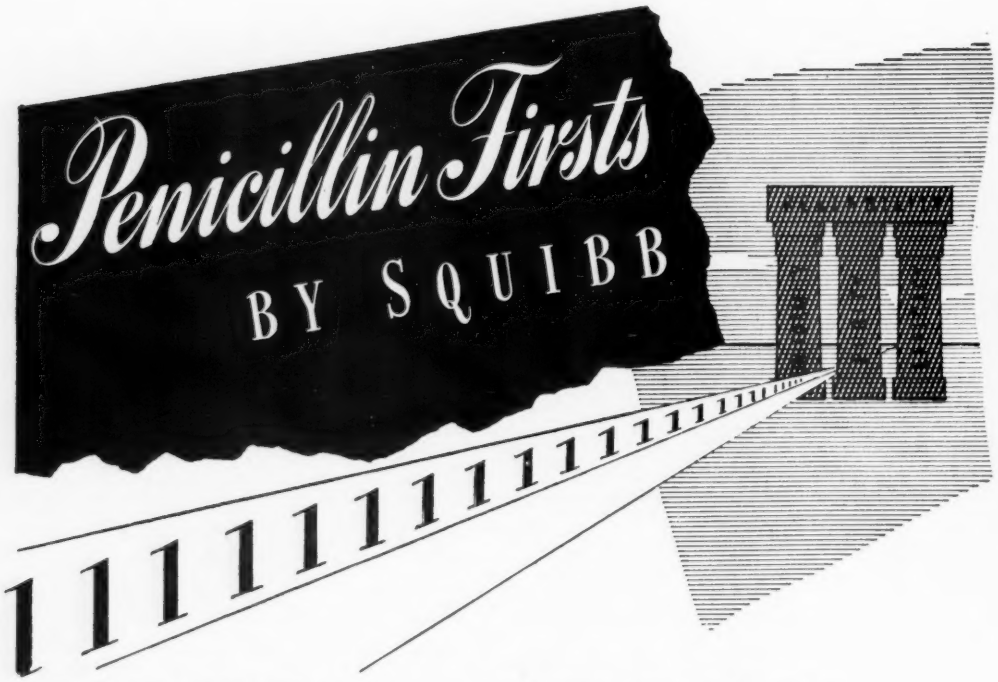

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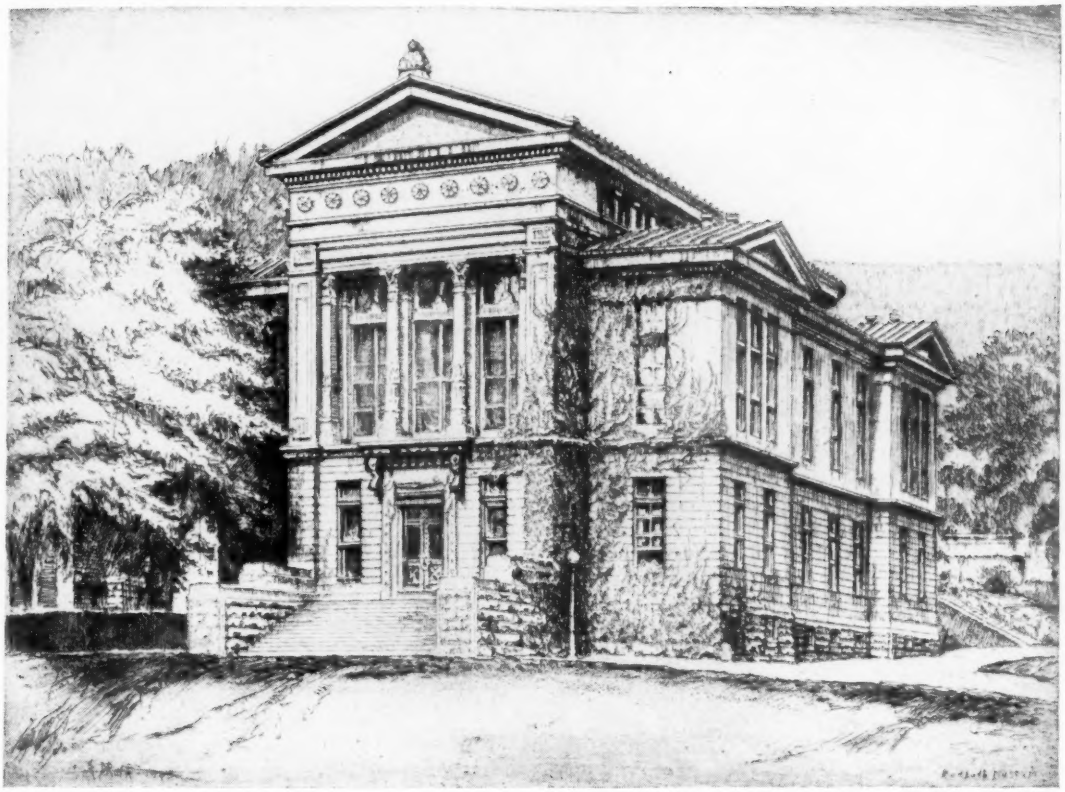


FROM AN ORIGINAL ETCHING BY ERNEST D. ROTH

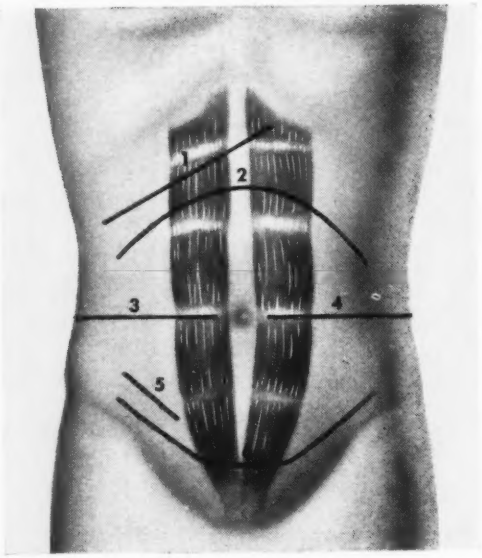
McGILL UNIVERSITY FACULTY OF MEDICINE, MONTREAL—This great medical school, alma mater of many noted physicians and specialists, was founded in 1823 as the Montreal Medical Institute and became McGill University Faculty of Medicine in 1829. Here Sir William Osler gained undying fame as a brilliant teacher of physiological pathology. McGill has an excellent medical museum and the finest medical library in Canada.

Learning is a constant, continuous and never ending process to members of the medical profession. New knowledge is sought as assiduously by the eminent and successful surgeon as by the humblest medical students. Through the discovery and presentation of new information regarding sutures and their use, Davis & Geck, Inc. seeks to perform a service of ever increasing value to the surgical world. In the following pages, some phases of this work, as well as certain aspects of D&G's production and quality control methods, are outlined briefly.

Incisions that Minimize Wound Disruption

AN IMPORTANT ADVANCE IN THE TECHNIC OF SUTURING

THE employment of operative incisions which offer maximal assurance against sutures pulling through the tissues eliminates one of the principal causes of wound disruption and lessens the possibility of postoperative herniation.



1. For gall bladder, common duct, head of pancreas.
2. Resection of stomach, transverse colon.
3. Resection of ascending colon, cecum, right sided lesions.
4. Descending colon, spleen and left sided lesions.
5. Appendectomy.
6. Pelvic surgery, resection of sigmoid.

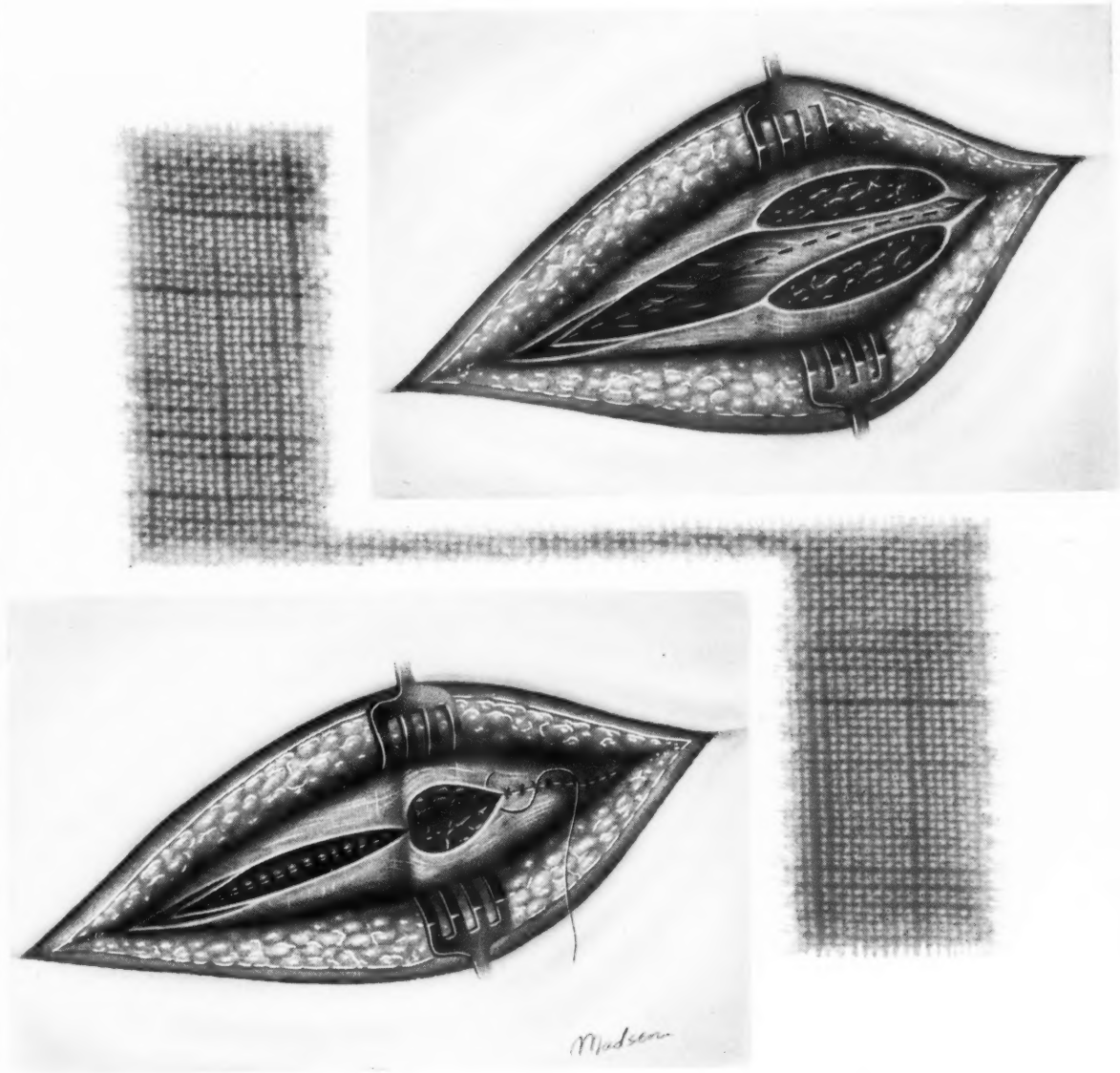
Sutures hold most securely if the connective tissues within the wound are approximated in such a manner that the sutures must pull against the fibres within these layers. This necessitates cutting the connective tissues parallel to the direction of their fibres which, in the anterior abdominal wall, is usually best accomplished through a transverse initial skin incision.

In the past, transverse abdominal incisions have not found wide acceptance because they necessitate cutting across muscles in which sutures hold poorly and almost invariably cause tissue necrosis.

In the new technic of suturing transverse incisions, no attempt is made to suture muscle—only the surrounding sheath. Approximation of the muscle edges is further aided by keeping the patient in a semi-reclining position with knees partially flexed.

Because of the favorable results attending increasing use of this technic, and the current interest in principles which may facilitate early ambulation, D&G will present a series illustrating the incisions, and methods of suturing them.

OBLIQUE OR TRANSVERSE INCISION FOR GALL BLADDER, COMMON DUCT, HEAD OF PANCREAS



If the costal angle is narrow the incision is made two or three finger breadths below the right costal margin and parallel to it. It is made almost transversely if the angle is wide. The right rectus muscle is cut transversely. The left rectus muscle can also be cut if this exposure is needed. Each muscle contains one or two small arteries and veins of comparable size which require ligation. The lateral muscles are divided parallel to their fibres. The peritoneum and posterior sheath are incised in a direction parallel to their fibres. The falciform ligament is divided in the middle and usually contains a small vessel which requires ligation.

The incision is closed by approximating the falciform ligament first. Next the peritoneum and the posterior sheath are sutured with interrupted sutures. The posterior sheath is sutured separately in the region of the falciform ligament. The muscles are not sutured. The anterior rectus sheath is approximated with interrupted sutures. Size 000 or 00 sutures can be used in both the posterior and anterior sheaths while slightly larger sizes can be used in the linea alba. Very fine sutures, 00000 to 000, may be used in the subcutaneous fat if desired. Drains are placed at the lateral edge of the wound.

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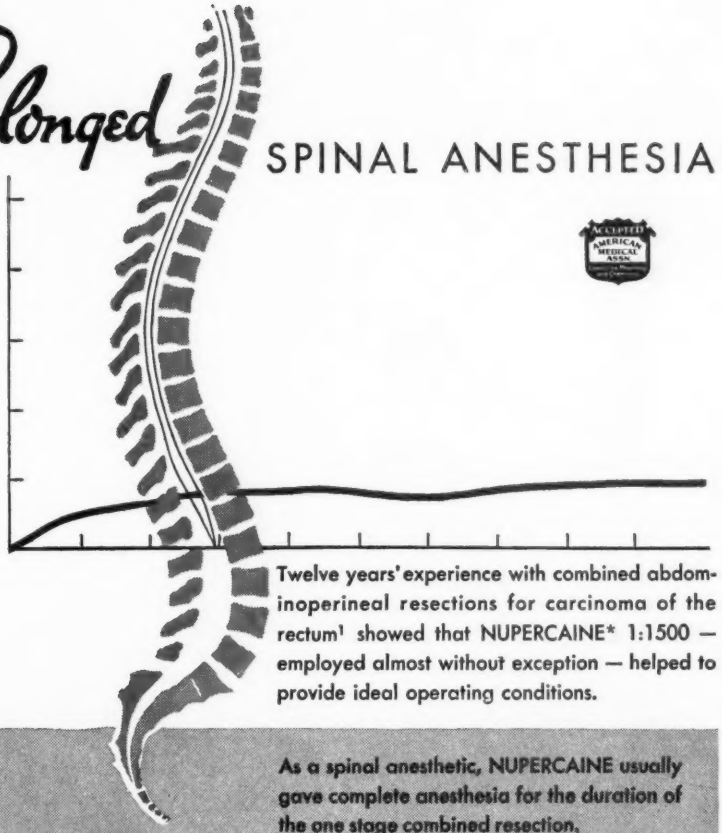

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[1]Coller, F. A. and Ransom, H. K.: Carcinoma of the Rectum. Conclusions Based on 12 Years' Experience with Combined Abdominoperineal Resection. Surg., Gynec. & Obst., 78:304,1944.

*Trade Mark Reg. U.S. Pat. Off. Word "Nupercaine" identifies the product as alpha-butyloxy-cinchoninic acid—gamma-diethyl-ethylenediamide-hydrochloride.

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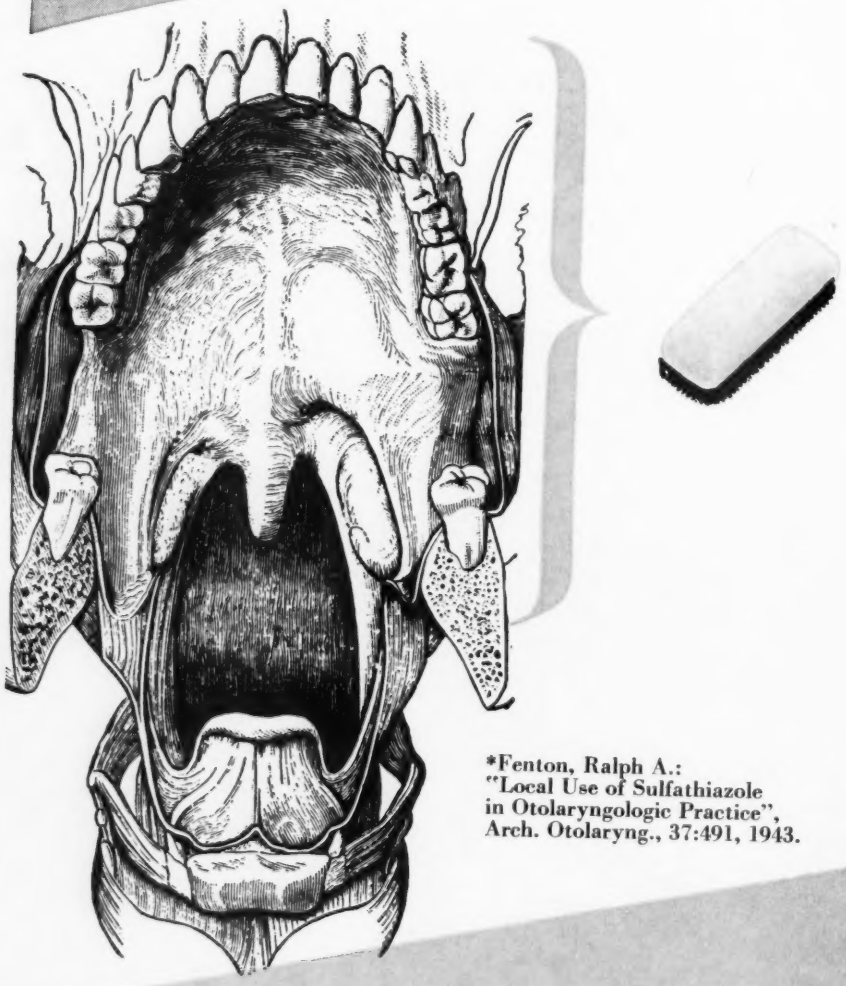

*Fenton, Ralph A.:
"Local Use of Sulfathiazole
in Otolaryngologic Practice",
Arch. Otolaryng., 37:491, 1943.

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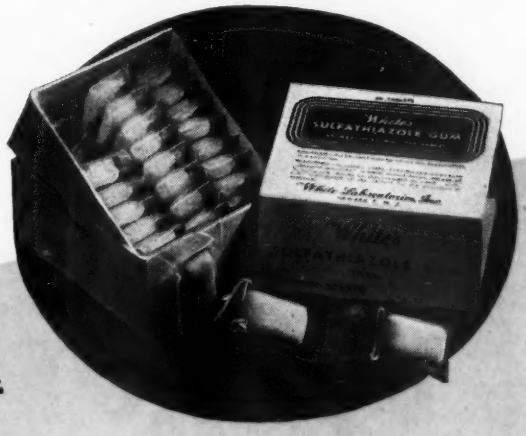

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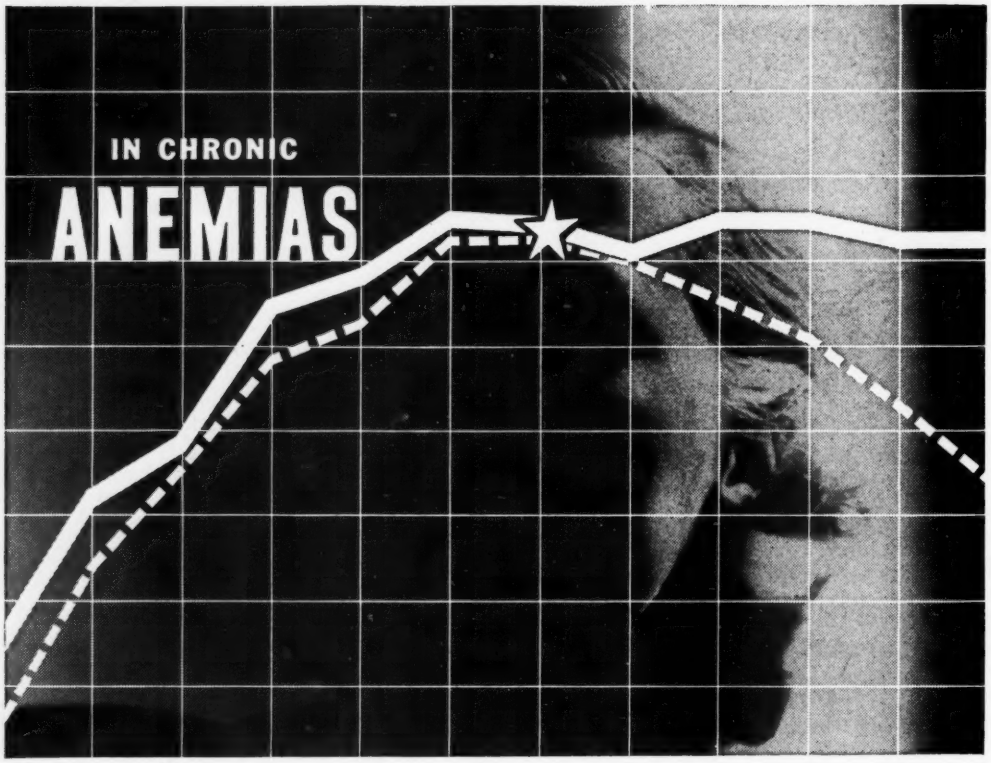

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*Gottlieb, R.: Whole Liver as an Adjuvant to Iron in the Treatment of Hypochromic Anemia, Canad. M.A.J. 47:456-460 (Nov.) 1942.

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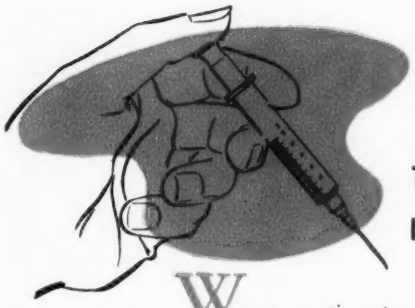

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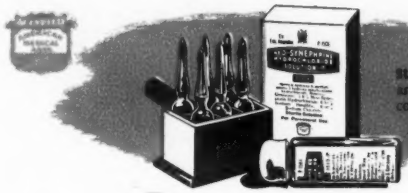

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*Rochberg, S.: *Anesth. & Analg.* 22:174, 1943.

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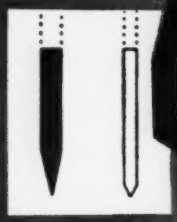

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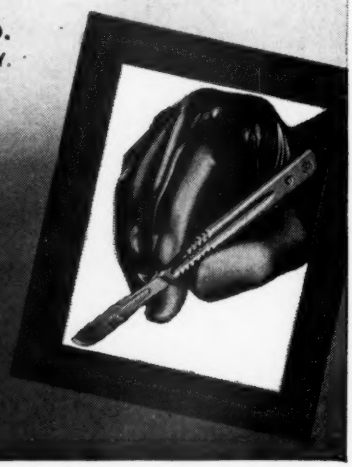

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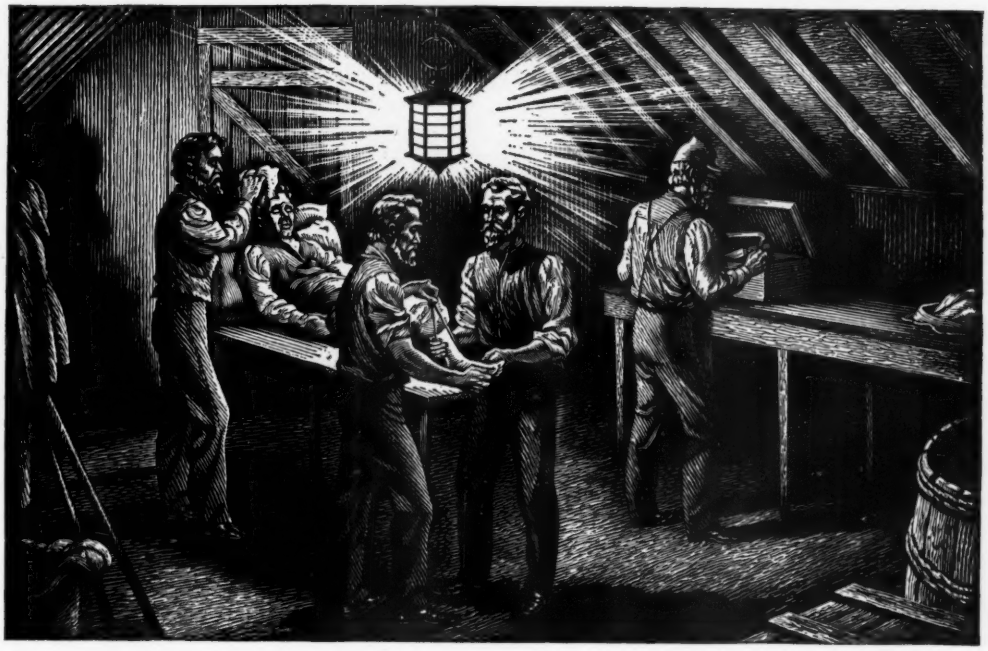

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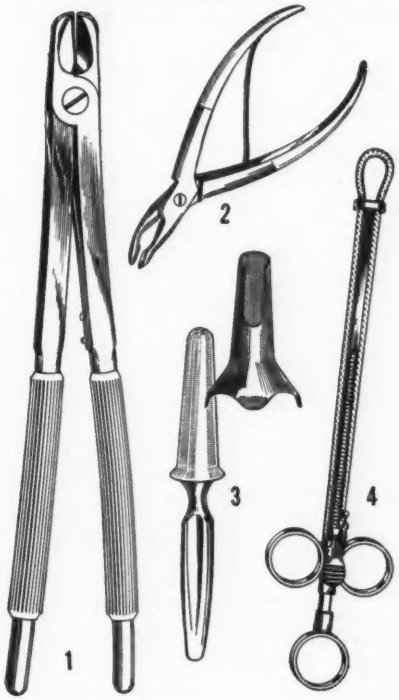

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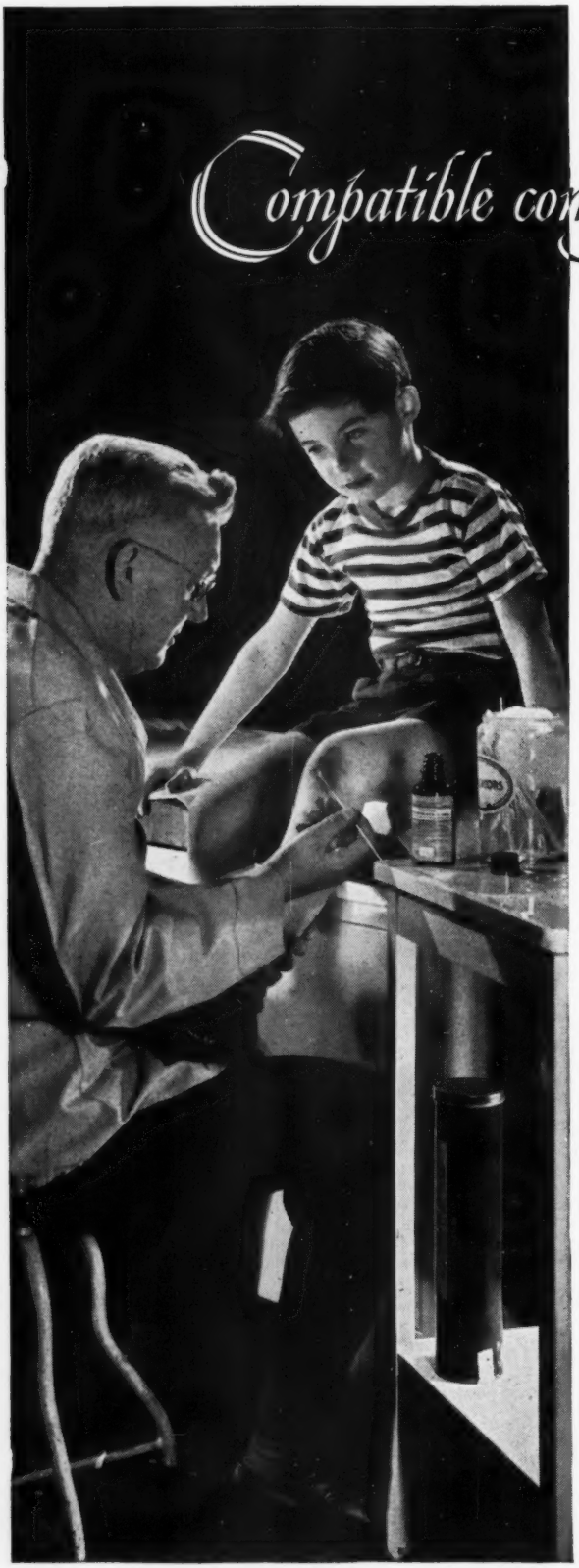

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SURGERY

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Original Communications

THE SIGNIFICANCE OF POLYMORPHONUCLEAR LEUCOCYTES IN GALL BLADDERS

JOHN P. MCKIBBIN, M.D.,* AND JOHN R. MCDONALD, M.D.,†
ROCHESTER, MINN.

THIS study was undertaken in an attempt to determine, if possible, the significance of polymorphonuclear leucocytes in the walls of thin-walled, noncalcareous gall bladders. There is almost universal agreement that the presence of polymorphonuclear leucocytes seen in a histologic section of a gall bladder wall is an indication of inflammation. It was noted that, when the occasional thin-walled noncalcareous gall bladder was removed at operation, the histologic appearance of the gall bladder wall would reveal the presence of polymorphonuclear leucocytes; yet gross examination would show an intact glossy mucosa and a wall thin enough and free enough from thickening and edema that, when the specimen was held to the light, it would be translucent. In an appendix, a similar appearance would be interpreted as representing subacute appendicitis. The question which naturally arose was, Is this an inflammatory process or is this a normal physiologic process that is being observed? Going further, perhaps the presence of polymorphonuclear leucocytes in the walls of other surgically removed specimens, such as the so-called strawberry gall bladder or gall bladders containing stones, is not in itself an indication of inflammation if not associated with other gross findings such as edema, thickening, inflammation of the mucosa, or the microscopic picture of large numbers of polymorphonuclear leucocytes, lymphocytes, and edema.

There is no mention in the literature of polymorphonuclear leucocytes being present in gall bladders that are not the site of inflammation. Noble[1] noted the presence of polymorphonuclear leucocytes and lymphocytes in the gall bladders of infants less than 1 year of age examined at necropsy. He expressed the belief that these cells were not present in sufficient numbers to indicate an inflammatory process and he specu-

Received for publication, Aug. 7, 1944.
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lated as to whether or not many of these minimal cell reactions seen in gall bladders that had been removed surgically from adults really represented a pathologic process, but he went no further.

Boyd[2] mentioned the presence of polymorphonuclear leucocytes in the more acutely inflamed gall bladders, but not otherwise. Smith and Gault[3] mentioned dilated capillaries with typical perivascular leucocytic infiltration in the acutely inflamed gall bladders but said nothing of their presence in chronic cholecystitis. McCartney,[4] in his description of mild chronic cholecystitis, stated that "there is no gross convincing evidence of disease, but in some instances of this type the microscopic examination reveals definite accumulations in the serosa with occasional polymorphonuclear leucocytes in the wall." Here is a well-stated description of the problem. Is the microscopic picture here actually a pathologic process or is it a physiologic one? Admittedly there is no gross evidence of inflammation.

Mentzer[5] found that in 75 per cent of 612 consecutive necropsy cases there were microscopic changes in the gall bladder, which he regarded as being pathologic. In these 612 necropsy cases, only 7.7 per cent of the deaths were due to gall bladder disease per se. The criterion for microscopic pathologic changes in the gall bladder was the presence of polymorphonuclear leucocytes or lymphocytic cells. On the basis of these findings, it would seem that there is a very high incidence of cholecystitis, or again, a physiologic function is being misinterpreted.

METHOD OF EXAMINATION

Twenty-five thin-walled noncalcareous gall bladders which had been surgically removed were selected for this study. These gall bladders grossly did not show any evidence of inflammation and, when they were held to the light, their walls were translucent. It was felt that, if the wall of the gall bladder was thin enough to transmit light in this manner, there could be very little fibrosis or edematous thickening.

For similar study and comparison, twenty-five so-called strawberry gall bladders and twenty-five gall bladders that contained stones were selected. In order that the iodized dye used in visualization of the gall bladder would not have to be considered as an irritative factor, twenty-five gall bladders were selected for which from the clinical history it was determined that an interval of at least twenty days had occurred between roentgenologic visualization and surgical removal of the gall bladder. Usually the interval between visualization and surgical removal is several days, and it was felt that concentration of the dye in the gall bladder might have some influence on the presence of the polymorphonuclear leucocytes in these gall bladders, because all of them were surgical specimens.

Ten gall bladders from dogs were examined to determine, if possible, whether a similar microscopic picture could be found. The dogs were

all in a state of excellent health, the gall bladders being obtained at the time heart-lung preparations were being made. It was felt that if polymorphonuclear leucocytes could be consistently found in the walls of these gall bladders, it would be difficult to conclude that these were examples of mild or subacute cholecystitis.

Ten gall bladders from fetuses between the ages of 3 and 5 months were also examined. This age was selected in order to obtain a gall bladder shortly after it had become a hollow organ but before it started to function as a gall bladder. Here it was felt that if the presence of polymorphonuclear leucocytes had to do with a metabolic function rather than an inflammatory process, one could postulate their absence from the recently developed nonfunctioning gall bladder of the fetus. All that remained to do was to prove this by microscopic examination.

Ten human appendices removed routinely during abdominal laparotomy and grossly not showing any evidence of inflammation were examined in a similar manner. Although the two organs have in common absorptive function, that of the appendix is immeasurably less than that of the gall bladder. If the polymorphonuclear leucocytes could not be demonstrated in the normally functioning appendix, this would tend to support the thesis that their presence in the gall bladder was metabolic and physiologic.

Lastly, a series of ten jejunums of dogs and a smaller number of noninflammatory human jejunums were examined with the thought of comparing the microscopic appearance of an organ of known highly absorptive function with that of the gall bladder, which is also known to have a definite absorptive function. The presence or absence of the polymorphonuclear leucocytes in the walls of the jejunum would be very important to support or discount the assertion of metabolic versus inflammatory function.

HISTOLOGY AND METHOD OF MICROSCOPIC EXAMINATION

Maximow and Bloom[6] divided the wall of the gall bladder into four layers: (1) a mucous layer consisting of a surface epithelium and a lamina propria, (2) a layer of smooth muscle, (3) a perivascular connective tissue layer, and (4) a serous layer covering part of the organ.

For the purpose of examining each section conveniently and accurately, it was decided to divide the wall of the gall bladder into three layers. The epithelium to the smooth muscle was one layer, the muscular layer was the second, and the tissue from the muscular layer, to and including the serosa, was the third layer.

Each of the three layers was then examined for the presence of polymorphonuclear leucocytes in the following positions: (1) in and around capillaries, (2) in and around lymphatics, and (3) in the tissue spaces. The type of polymorphonuclear leucocyte present was not determined in general, although eosinophiles were noted because of their consistent presence in the walls of the appendix.

Lymphatics could not be positively identified, but vessels whose walls consisted only of endothelial cells and whose lumina did not contain any erythrocytes were assumed to be lymphatics. In general, what was considered most important was the presence or absence of polymorphonuclear leucocytes regardless of location, except, of course, their association in normally accepted numbers mixed with erythrocytes in blood vessels. The same scheme was followed in examining microscopically the slides of jejunal and appendical tissue.

For simplification, the number of polymorphonuclear leucocytes in a single low-power, dry, microscopic field in any of the three layers or any of the three locations was classified numerically as occasional, few, and many. An occasional polymorphonuclear leucocyte would indicate one to three per low-power dry field, a few would indicate four to eight per low-power dry field, and many would indicate eight or more per low-power, dry, microscopic field.

HISTOPATHOLOGY

In the thin-walled noncalcareous gall bladders, polymorphonuclear leucocytes were found to be present in every section (Table I). In twelve of the microscopic sections many polymorphonuclear leucocytes were found to be present in at least one of the layers of the gall bladder. In eleven of the cases there were only a few, and in two cases only an occasional polymorphonuclear leucocyte was present. Many times polymorphonuclear leucocytes were present in one of the layers but in none of the others in the same histologic section (Fig. 1).

A similar microscopic picture was found in the strawberry gall bladders except that, in those sections in which many polymorphonuclear leucocytes were present, the total number present in a single field was greater than was found in the sections of thin-walled noncalcareous gall bladders. In eleven of these gall bladders there were many polymorphonuclear leucocytes, in nine there were a few, and in five there was only an occasional polymorphonuclear leucocyte (Fig. 2).

TABLE I

POLYMORPHONUCLEAR LEUCOCYTES IN THE WALL OF GALL BLADDERS

	SPECIMENS	CONTAINING LEUCOCYTES		
		MANY	FEW	OCCASIONAL
Thin-walled noncalcareous*	25	12	11	2
Strawberry gall bladder*	25	11	9	5
Gall bladders containing stones*	25	9	12	4
No dye*	25	6	12	7
Dog gall bladder	10	2	5	3
Fetal gall bladder	10	0	0	0
Dog jejunum	10	2	2	5

*All these gall bladders were surgically removed.

Nine of the gall bladders that contained stones had many polymorphonuclear leucocytes in the wall, twelve had a few, and four had an

occasional polymorphonuclear leucocyte. The walls of all these gall bladders were thickened and fibrotic microscopically (Fig. 3). Grossly, none of the calcareous gall bladders showed evidence of acute inflammation.

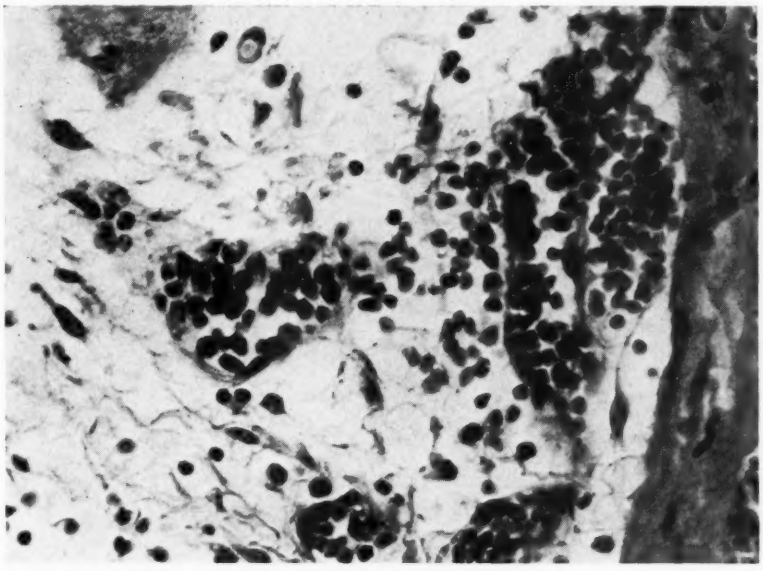

Fig. 1.—Wall of thin-walled noncalcareous gall bladder. Note the presence of occasional intracapillary polymorphonuclear leucocytes (hematoxylin and eosin ×435).

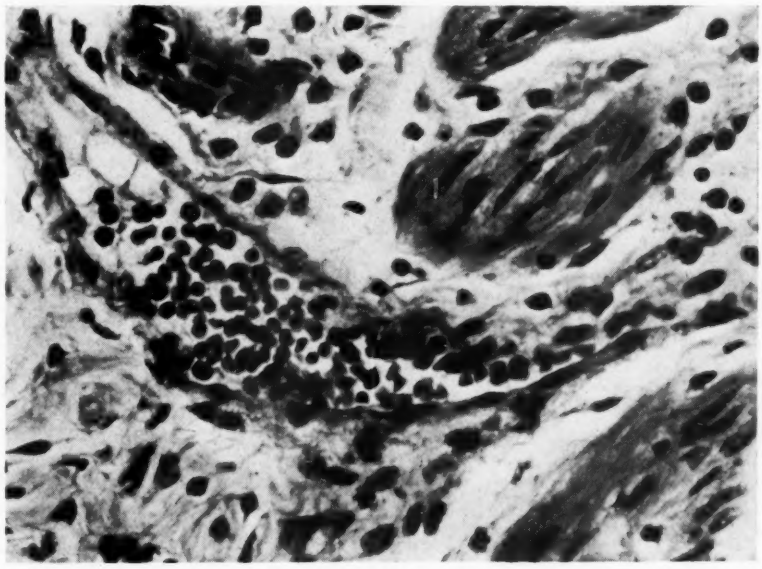

Fig. 2.—Wall of strawberry gall bladder. Many polymorphonuclear leucocytes are present in the capillaries in the muscular layer (hematoxylin and eosin ×435).

Among the gall bladders selected for having an interval of twenty days or more between roentgenographic visualization with iodized dye

and operation, six had many polymorphonuclear leucocytes, twelve had a few, and seven had only occasional polymorphonuclear leucocytes (Fig. 4).

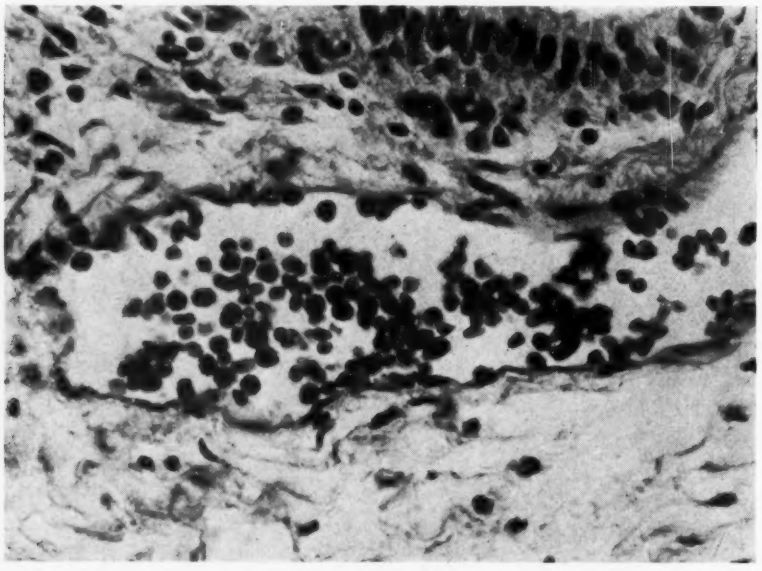

Fig. 3.—Wall of calcareous gall bladder. Many polymorphonuclear leucocytes can be seen in the capillary. Diapedesis is evident (hematoxylin and eosin ×435).

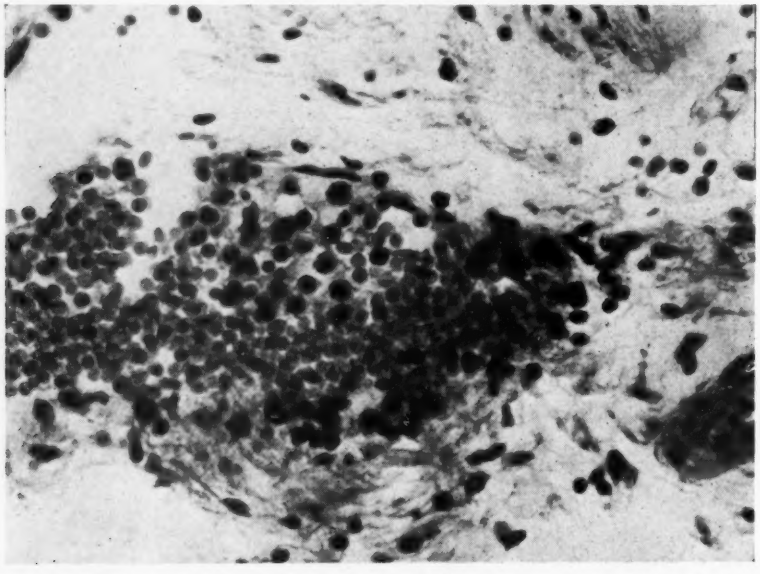

Fig. 4.—Wall of gall bladder. This patient had not been given dye recently. Many polymorphonuclear leucocytes can be seen in the capillary (hematoxylin and eosin ×435).

In two of the ten normal gall bladders removed from dogs there were many polymorphonuclear leucocytes, in five there were a few, and in three there were occasional polymorphonuclear leucocytes (Fig. 5).

No polymorphonuclear leucocytes were seen in any of the sections of the fetal gall bladders.

The ten noninflamed appendices did not show a microscopic picture similar to that of the gall bladders. The polymorphonuclear leucocytes so consistently found in the capillaries of the gall bladder wall, often in greater numbers than the associated erythrocytes, were absent from the capillaries of the wall of the appendix. When larger vessels were sectioned, they showed polymorphonuclear leucocytes to be present only in a normal ratio to the erythrocytes present. There were usually numerous eosinophiles among the many lymphocytes.

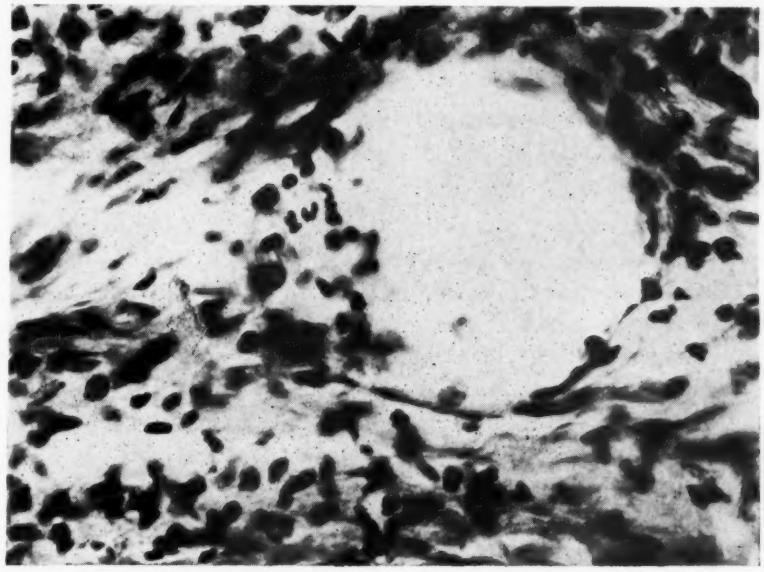

Fig. 5.—Wall of thin-walled noncalcareous gall bladder from a dog. Note the intraluminal polymorphonuclear leucocytes (hematoxylin and eosin ×435).

In the sections made of the jejunal specimens of human and canine origin, a picture of numerous intracapillary polymorphonuclear leucocytes in greater than normally expected numbers was seen. This was not always the case but consistently enough to be comparable to the sections of gall bladder in microscopic appearance.

COMMENT

The outstanding finding was not only the consistent presence of polymorphonuclear leucocytes in the thin-walled noncalcareous gall bladders but their presence in similar numbers in all the gall bladders examined except the nonfunctioning fetal gall bladders. These findings are not remarkable when compared with Mentzer's 612 necropsy cases in which he found evidence of microscopic inflammation in the form of polymorphonuclear leucocytes and lymphocytic cells in 75 per cent of the cases, in 7.7 per cent of which the patients died of gall bladder disease.

Eighty-two per cent of the surgically removed gall bladders in our study showed either many or few polymorphonuclear leucocytes in the wall. This excludes those gall bladders which contained only occasional polymorphonuclear leucocytes (Table I). Ordinarily all these gall bladders would be considered as showing evidences of inflammation. This figure is comparable to that of Mentzer.

As has been previously mentioned, none of these gall bladders had the gross appearance of acute inflammation and it does not seem too difficult to ascribe the presence of the polymorphonuclear leucocytes to a metabolic function rather than an inflammatory process, especially when the same microscopic picture could be seen in the gall bladders of dogs (Fig. 5). (Seventy per cent of the gall bladders removed from dogs, when examined microscopically, showed many or a few polymorphonuclear leucocytes.) In addition, if it is accepted that these polymorphonuclear leucocytes are serving a metabolic function, their complete absence from the nonfunctioning fetal gall bladders gives added weight to this interpretation.

Their absence in the noninflammatory appendix and their consistent presence in the human and canine jejunums, the former an organ of low absorptive function in comparison with the latter, which is of absorptive function, would also seem to indicate a metabolic function. Mackey[7] referred to this seemingly analogous function of the intestinal epithelium and the known active resorption carried out by the gall bladder. Why could not a similar microscopic picture be indicative of a similar physiologic function?

Of all the gall bladders examined, the strawberry gall bladders appeared to contain the greatest number of polymorphonuclear leucocytes in their walls (Fig. 2). This is significant in that the increased number of polymorphonuclear leucocytes in such cases could represent an attempt to carry out a more rapid physiologic process, which is occurring to a lesser extent in all the other functioning gall bladders examined.

Finally, is there any proof to support this interpretation of metabolic function of these polymorphonuclear leucocytes in the gall bladder? Boyd,[8] in his investigations of the pathology of the gall bladder, found that the endothelium of blood vessels in the gall bladder wall contained streaks of material which stained red with scarlet red. He also found this material in tissue inflammatory cells but did not mention polymorphonuclear leucocytes. Therefore, a series of surgically removed gall bladders were studied microscopically. The fresh frozen-section technique was used and the sections were stained with scarlet red for lipoid. This was done without fixation of tissue to avoid losing fat or lipoid. These sections showed the polymorphonuclear leucocytes to contain pale-staining granules, which when examined under the polarizing microscope were not doubly refractile. This would indicate that the granules were not cholesterol or cholesterol esters, but it seemed suf-

ficient proof that the polymorphonuclear leucocytes were carrying some type of lipoid and this was what was sought. This was not identification of the lipoid but proof of a function, metabolic in type to account for the presence of the polymorphonuclear leucocytes in the gall bladder for a purpose other than inflammatory.

Although Mackey[7] did not mention the presence of polymorphonuclear leucocytes, he noted the presence of lipoid in the walls of gall bladders and stored in the stromal macrophages. He expressed the belief that this is a normal process, analogous to the process of resorption carried out by the intestinal epithelium and similar to resorption of other substances known to be carried out by the lining of the gall bladder.

CONCLUSIONS

1. The presence of polymorphonuclear leucocytes in the walls of the gall bladder, when examined microscopically, is not in itself an indication of inflammation when not associated with other signs of inflammation and should not be interpreted as such.

2. These polymorphonuclear leucocytes are serving a metabolic function rather than an inflammatory function when not associated with other signs of inflammation.

3. The iodized dye used in the preoperative roentgenographic visualization of the gall bladder does not have any association with the presence of the polymorphonuclear leucocytes in surgically removed specimens.

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GASTRIC SCHWANNOMA

Report of a Large Intragastric Lesion Simulating a Bezoar

Julio Sanguily, M.D., and Francisco Leon Blanco, M.D.
Havana, Cuba

NONEPITHELIAL benign tumors of the stomach are very rare; even rarer are neurogenic tumors. However, Mines and Geschickter believe that approximately 10.9 per cent of benign tumors of the stomach are neurofibromas.

Ransom and Kay described, in 1940, seven lemmomas of which three were associated with other gastric disturbances and were discovered by accident.

The type of tumor here described is known in the medical literature by many names following the different microscopic aspects which it may present and the different descriptive opinions explaining its nature. Thus, Penfield considering it of connective tissue origin calls it perineural fibroblastoma; Verocay associates it with the nervous tissue and designates it neurinoma; the type due to Schwann's cells is called schwannoma (Masson) and lemmoma (Haeckel); Roussy, Lhermitte, and Cornill considering Schwann's cells as neuroglic cells (peripheric neuroglia) termed these tumors peripheric gliomas.

As it is not the object of this presentation to discuss the histogenesis and exact histologic picture of schwannomas, we suggest that those interested in this phase of the subject consult the brilliant works by Del Rio Ortega, Penfield, and Masson.

Our case is interesting because of the size of the tumor, because of its projection within the gastric cavity as a pedunculated neoplasia, and because of the several diagnostic possibilities to be considered.

The clinical report with all details is given in Case 1.

CASE REPORT

Case 1.—The patient, J. G. M., 58-year-old Negro woman, was referred from the department of digestive diseases of the Municipal Hospital, Gral. Freyre de Andrade, to our surgical service. For one year she had had a discomfort in the left hypochondrium which extended to the epigastrium and felt like a ball. This was associated with indigestion, that is pyrosis, nausea, and a constant feeling of distention. She was constipated and suffered with flatulence. However, appetite was good. There was no pain. The epigastric mass changed position, and when it was on the right side the patient became very uncomfortable but was relieved by displacing it, especially when she had eaten. She rarely vomited but had lost much weight.

She looked rather old, the tongue was coated, and there was marked oral sepsis. The intensity of the heart tones and rhythms were normal. Over the apex there was a systolic murmur. The lungs were normal. On palpation of the abdomen

Read at a meeting of the National Surgery Society, May 26, 1944.
Received for publication, Aug. 8, 1944.

there was found in the left hypochondrium and under the costal border a hard, smooth, movable tumor, which could be displaced if pressure was made on it. Because of these characteristics and its position, this tumor could be easily confused with the spleen, although it was not typical of a spleen. The size of the liver was normal and the rest of the abdomen negative. There was lack of adipose and the skin was wrinkled and dehydrated. The blood pressure was 140/95; pulse was 72.

The preoperative laboratory examinations were all normal.

Fig. 1.—Anteroposterior view with barium meal. The stomach never appeared filled with barium. The only free transit was through the lesser curvature.

The gastrokymogram showed an increase in the motor function and a decrease in the secretory function with hypochlorhydria at the beginning and anachlorhydria at the end. Occult blood was positive (++). The pylorus apparently opened with duodenal biliary reflux.

The roentgenogram demonstrated a foreign body occupying the whole gastric cavity, resembling a bezoar by the fluoroscopic and radiographic study (Figs. 1 and 2).

From this history it could not be determined that the patient had been in the habit of chewing hair or eating food rich in resin; she had never eaten caimito, sapote (Cuban fruit), or persimmons, or has never lived out in the country.

In spite of the fact that there was nothing in her history to suggest a gastric bezoar, we accepted the opinion of the radiologist, Dr. Padron, and operated upon the patient in search of the intragastric foreign body. The patient was previously prepared by hydration and repeated gastric lavage. The operation was performed Nov. 10, 1943. A midline supra-umbilical incision was made under spinal anesthesia (pantocain 0.018 gr.).

Fig. 2.—Lateral view of the stomach with barium meal.

On opening the abdominal cavity it was demonstrated by palpation that the lesion was a pedunculated intragastric tumor. A longitudinal incision was made in the anterior wall of the stomach, after carefully walling off the peritoneal cavity (Fig. 3). After opening the stomach a large tumor occupying the entire gastric cavitiy was visualized. It was solid, dark red, and was attached by a pedicle to the

posterior wall of the fundus, from which it extended into the gastric cavity (Fig. 3). The tumor had assumed the shape of the stomach. By exerting traction on the tumor it was possible to exteriorize the pedunculated attachment of the tumor to the posterior wall of the fundus. The gastric mucosa covering the tumor in its entirety appeared thick because of an associated gastritis. With the the scapel the mucosa was incised around the perimeter of the pedicle. The tumor was then easily removed. Careful hemostasis was secured, following which the mucosa of the

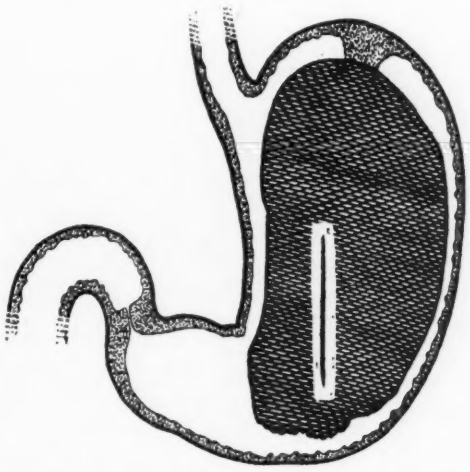

Fig. 3.—Schematic drawing to show the incision, shape, and situation of the tumor.

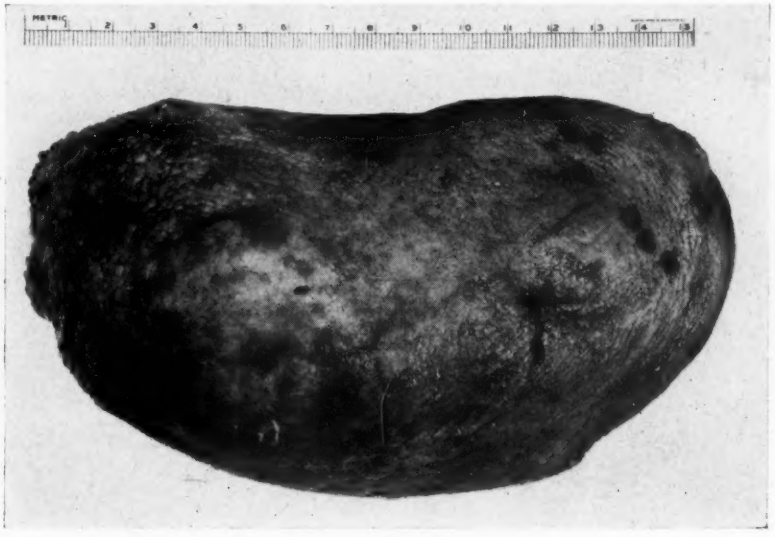

Fig. 4.—The tumor covered totally by gastric mucosa. Signs of chronic gastritis are seen in the lower pole.

superior and posterior walls of the stomach was sutured by means of a fine continuous intestinal catgut suture. The posterior wall was placed to its normal position, and it was observed that the suture of the mucosa remained in a high position and extended from right to left. The posterior wall of the stomach had not been opened or included in the sutures, as evidenced by the fact that the serosa on the posterior surface was intact. Before the gastric wound was closed,

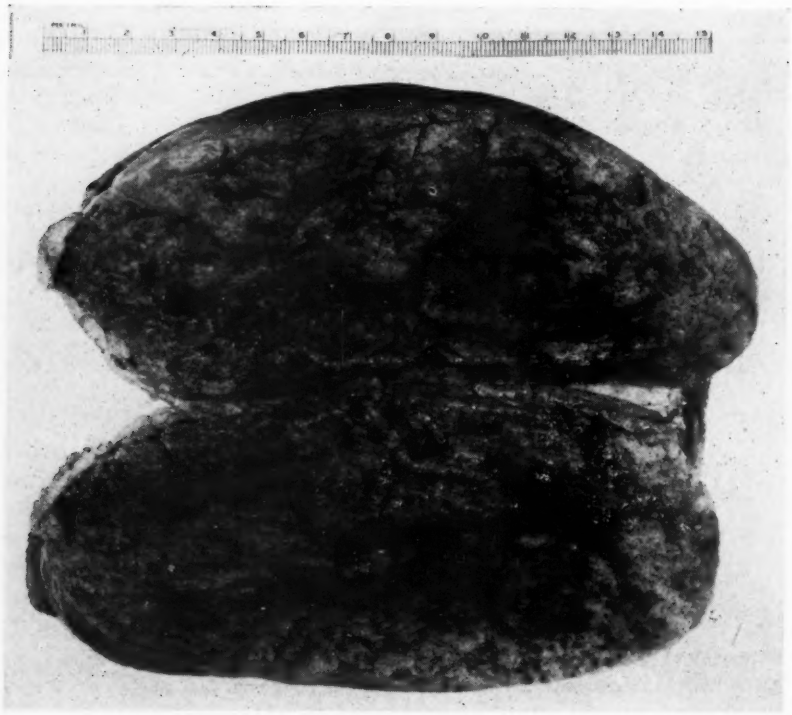

Fig. 5.—The tumor opened in the middle longitudinally. Notice the multiple pseudocystic cavities.

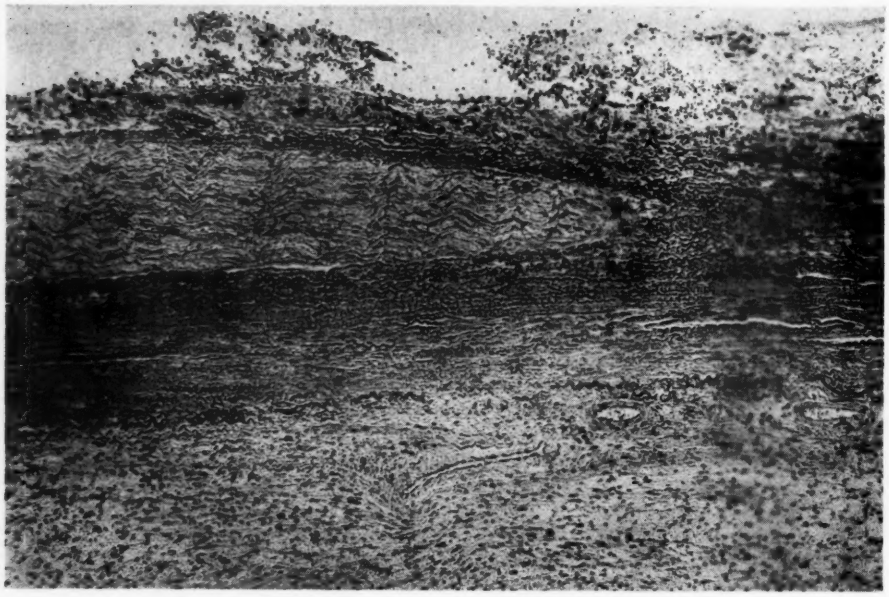

Fig. 6.—Microphotograph of the capsule of the tumor and the superficial layer of it. Notice a small nerve branch in the capsule (magnification ×80).

incision of the gastric cavity was irrigated with hot saline solution which was aspirated. The gastrotomy opening was closed by a complete catgut suture and a seroserosal suture of linen, strengthened with several Cushing sutures. The suture line was dusted with sulfanilamide crystals, and the stomach replaced in its anatomic position. A Levin duodenal catheter was introduced for gastric decompression. Dextrose and saline solution and vitamin C were administered intravenously, and no food was allowed by mouth.

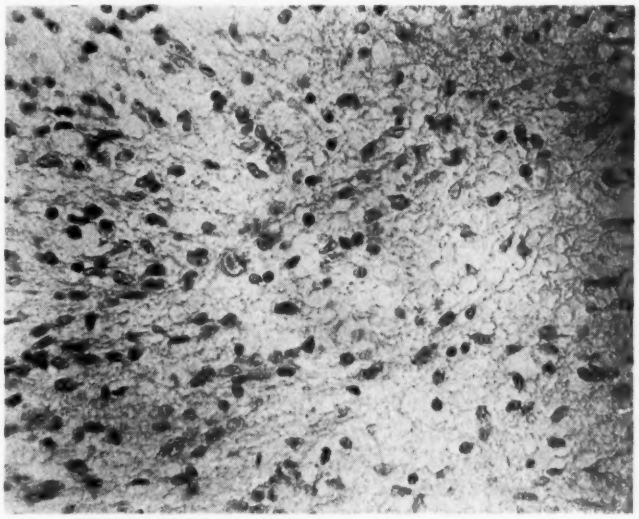

Fig. 7.—Microphotograph demonstrating myxomatous degeneration (magnification ×400).

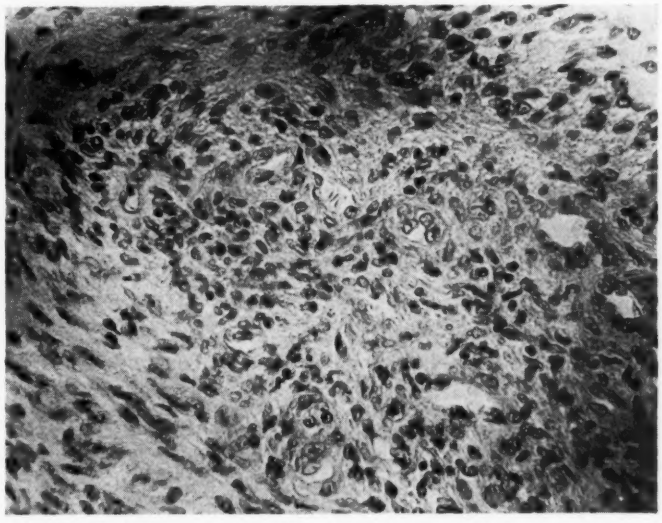

Fig. 8.—Microphotograph of the tumor showing a marked polymorphism of the cells. Nuclei and cells are scattered in different planes.

Pathologic Findings.—Macroscopic characters were: size 17 by 9 by 5 cm.; weight: 580 Gm. The tumor occupied most of the gastric cavity, and was movable, except where it was attached to the posterior wall by a pedicle one inch in diameter. The pedicle was centrally formed by connective tissue through which the tumor's

vessels ran. On the outside the rest of the pedicle was only gastric mucosa. With the exception of the pedicle the tumor was completely covered with gastric mucosa, and was separated from the mucosa by a thin connective tissue membrane (Fig. 4). On cutting, the consistence of the tumor felt soft; the surface appeared white yellowish with hemorrhagic points (Fig. 5).

Histologic Diagnosis.—The histologic diagnosis by one of us (F.L.B.) was schwannoma.

Postoperative Course.—The postoperative treatment (Figs. 6, 7, and 8) which was routine for these cases, consisted of the administration of small amounts of albuminous water, with periodic aspirations through the Levin catheter for several days.

The postoperative condition of the patient was normal but on the tenth day when the patient was ready to be discharged from the hospital after the wound was well healed and the sutures removed she had such a severe hematemesis that it appeared she might succumb, but with the quick assistance of an intern the acute anemia was quickly overcome. She was given a citrated blood transfusion, gastric lavages with hot physiologic saline solution, large doses of vitamin K, and an indwelling duodenal catheter was introduced. The gastric hemorrhage quickly stopped and the patient was discharged from the hospital nineteen days after the operation.

We have seen the patient recently; she is well and has gained twenty pounds in weight.

COMMENTS

The radiologic picture of this benign tumor of the stomach could easily be confused with any intragastric foreign body.

The clinical symptoms of these two conditions are not sufficient for an accurate diagnosis, which is quite difficult without radiologic examination. Benign tumors of the stomach are rare and only in the large ones can the diagnosis be suspected. A reason for making a mistake in the diagnosis in the case described was the unusual and peculiar location of this tumor. Most benign tumors are found at the greater curvature, at the fundus, or at the pyloric end of the stomach. Of all benign tumors, the one most easily diagnosed is the gastric polypus, because of its gastric symptoms and because they degenerate and ulcerate.

When benign gastric tumors are located near the pylorus they produce early symptoms of stenosis, which suggest to the physician the need for a radiologic investigation. On the other hand, if the benign tumors are small and away from the pylorus, they may present fewer or no gastric symptoms. Regarding gastric evacuation, we know that large-sized pedunculated tumors produce certain inertia of the muscles, and therefore produce a slow gastric evacuation; on the contrary, small-sized tumors excite the muscles and the evacuation is rapid. In the first group the stomach is hypotonic, whereas in the second it is hypertonic.

When, on examination of this patient, a tumor was found in the region of the stomach, even though there were few digestive symptoms, gastric x-ray was obtained. An intragastic lesion occupying the entire cavity was found. Logically, the first diagnosis was a gastric bezoar.

A gastric neoplasm seemed unlikely because of the few gastric symptoms and the history of its having been present for a year. On the other hand, the clinical picture in gastric bezoars develops insidiously and there are few, if any, symptoms and therefore gastric bezoars seemed likely.

Bezoars, as we all know, are concretions, like stones, which are found in the stomach of certain animals fed with food rich in resin. In ancient times these concretions were removed from the stomach of goats, camels, and cows, and sold as a medicament and the antidote of certain poisons. That is exactly what the Persian word *bezoar* means, literally translated, "protecting against poison."

Bezoars occur in those people who eat a great deal of caimito, sapote, raisins, etc., or vegetables rich in resins or fiber. Coming in contact with the hydrochloric acid of the stomach they are precipitated forming such large and hard nucleus that they cannot pass through the pylorus and must be removed operatively.

Bezoars formed by vegetable elements are called phytobezoars and those found in psychopathic persons in the habit of chewing and swallowing hair are called trichobezoars; a mixture of both being trichophytobezoars.

These foreign bodies and benign tumors of the stomach have similar clinical pictures and both require surgery. When the benign tumor is pedunculated and away from the pylorus, a relatively simple operation is all that is necessary, as in our case.

If the tumor is near the pylorus, producing stenosis, or if there is the slightest possibility of cancer, a partial gastrectomy is recommended as a rule.

When the tumor does not extend into the gastric cavity an elliptical incision is made through the gastric wall around the tumor, removing it in toto. The opening of the stomach is then closed in layers. Gastric polyposis, which does not disappear after medical treatment, requires total gastrectomy in some cases, because a polypus must be considered as a premalignant lesion.

An interesting feature of the case was the hypertrophic inflammatory reaction of the gastric mucosa covering the tumor. Also interesting was the fact that as the tumor was growing it assumed the shape of the gastric cavity and in spite of its size and weight the pedicle could hold it perfectly and the tumor was not resting on the gastric fundus. Undoubtedly if this had happened, the symptoms would have been more serious, and the patient would have sought treatment sooner.

The postoperative hemorrhage in this patient, ten days after the operation, risked her life. There are two explanations for this complication. In the first place there may have occurred a dehiscence of the gastric mucosa suture at the site of the tumor. Although the suture was high in the fundus of the stomach, it is possible that digestive

action of the hydrochloric acid dissolved the catgut and started the bleeding in spite of the perfectly made hemostasis at the time of the operation. On the other hand, an avitaminosis because of insufficient diet before, and even more so after, operation may have been a responsible factor in causing the massive gastric hemorrhage.

In the treatment of hematemesis following gastric surgery, we use blood transfusion, recommending it as an extraordinary and efficient hemostatic and antishock measure.

Gastric lavages with Levin catheter with lukewarm serum have given us good results, added to an adequate vitamin therapy. We want to make clear that the most important fact is the early attention given to a patient as soon as the first symptom of hemorrhage appears and that is why Levin's catheter used permanently is a safe treatment because by periodic aspiration and gastric lavage it is possible to stop any bleeding early.

SUMMARY

1. A case of a large-sized benign tumor of the neurogenic type (schwannoma) is reported.

2. Because of its radiologic features and few symptoms, it was confused with an intragastric bezoar.

3. The gastric neoplasm was removed transgastrically through an anterior gastrotomy. In spite of careful hemostasis and an otherwise normal convalescense, a massive gastric hemorrhage occurred on the tenth postoperative day. Convalescence otherwise was normal.

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PERFORATION OF THE RECTOSIGMOID

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WE ARE reporting from our service at the Metropolitan Hospital three cases of traumatic perforation of the rectosigmoid, one produced by rectal biopsy, one by the administration of a high colonic irrigation, and the third by the administration of an enema. All patients were operated upon, and two recovered, but one died.

CASE REPORTS

CASE 1.—W. W., a man, 67 years old, was admitted Jan. 20, 1941, with a chief complaint of rectal bleeding. Present illness had started eight months previously when the patient first noticed constipation and blood when straining at stool. Bleeding was not profuse nor was it painful. Within this period, there was a weight loss of twenty-seven pounds.

In general, the past history was essentially negative. Laboratory data were within normal limits. Rectal examination revealed the presence of external hemorrhoids and internal prolapsed hemorrhoids. In view of the history of constipation coinciding with the beginning of the rectal bleeding and weight loss, the possibility of a malignancy of the rectosigmoid or descending colon was entertained, and a sigmoidoscopy was recommended. This was done in the operating room preceding the removal of the hemorrhoids.

Under caudal anesthesia, a sigmoidoscope was passed gently to the 20 cm. mark. Examination revealed a polypoid mass about 15 cm. from the anal opening. Attempts to grasp this mass through the sigmoidoscope were unsuccessful, and the sigmoidoscope was removed. A finger was then inserted into the rectum and by applying pressure, the polypoid mass was reached, the finger hooked around it, and the mass drawn into the anal canal where it was grasped with an Allis forceps, and a section of the mass was excised for biopsy. The hemorrhoids were then excised in the routine manner (clamp and suture method).

During the afternoon of the operative day, the patient complained of lower abdominal pain. There was slight distention but no rigidity. The next day, there was marked tenderness. An X-ray taken on this day showed free air beneath the diaphragm, with moderate distention of the bowel and several fluid levels in the distended loops. Diagnosis was made of pelvic peritonitis secondary to traumatic perforation of the bowel. The patient was prepared for operation. The abdomen was entered through a left lower rectus incision. The small bowel and upper sigmoid appeared clean and not inflamed. The pelvic colon was exposed, and a longitudinal perforation ¾ inches in length was located anteriorly on the rectosigmoid just above the pelvic floor. This was closed with two rows of sutures. A rectal tube was passed through the anus and guided to a point 5 inches above the perforation. Fifty cubic centimeters of 5 per cent neoprotosil (at that time the sulphonamide preparation employed for peritoneal implantation) were instilled into the area, and the abdomen was then closed. Postoperatively, a Miller-Abbott tube

Received for publication, Nov. 16, 1944.

was passed and connected to a Wangensteen suction apparatus to maintain deflation of the bowel. In addition, sulfathiazole was given. The patient received blood transfusions and parenteral fluids.

Subsequently, the patient's temperature ranged between 100 and 103°F. On the fourth postoperative day, he had two bowel movements. Examination of the wound at this time showed marked purulent discharge and a partial dehiscence of the upper two-thirds of the abdominal wound. The wound was packed and strapped with flamed adhesive strips. The packing was removed on the sixth postoperative day, and new packing and adhesive strips were applied. The Miller-Abbott tube and the Wangensteen suction were working adequately, and the abdomen was not distended. By the ninth postoperative day, the temperature was normal, and the Miller-Abbott tube was removed. The wound appeared clean and was granulating. The packing was removed, but the adhesive strips were reapplied. The wound healed slowly but steadily, and the patient was dicharged on the fifty-fourth postoperative day. Two months after discharge, the patient had no complaints, and the scar was well healed and solid.

The pathologic report of the biopsy of the rectum was hyperplastic glandular rectal mucosa, with no evidence of specific disease.

CASE 2.—M. B., a man, aged 63 years, was admitted March 6, 1944, with a chief complaint of severe abdominal pain. This patient was being treated at another hospital for hypertensive cardiovascular disease, generalized arteriosclerosis, osteoarthritis of hands, old cerebral thrombosis and right hemiparesis, and bilateral inguinal hernia.

Late in January, he was found to have hematuria, and cystoscopy and intravenous urography were performed but were essentially negative. March 6, 1944, the patient was being prepared for a repetition of the cystoscopy. A colonic irrigation was given as part of the preparation. During the time this irrigation was given, and, subsequently, he complained of severe abdominal pain. Later on, he began to vomit coffee ground material, and examination revealed a boardlike rigidity of the abdomen. A tentative diagnosis of perforated peptic ulcer was made, and the patient was transferred to the Metropolitan Hospital.

When first seen, this patient appeared acutely ill. He was markedly emaciated and in acute agony. He was lying on his left side with his knees drawn up and his trunk sharply flexed. Abdominal examination revealed generalized boardlike rigidity, tenderness, and rebound tenderness throughout the abdomen. Bilateral inguinal hernias were reducible and not particularly tender. Rectal examination showed tenderness in both iliac fossae. No masses were palpable. Diagnosis considered was spreading peritonitis due to perforated viscus, resulting from the high colonic irrigation; perforated peptic ulcer.

The patient was prepared for immediate surgery. Under local anesthesia, the abdomen was opened through a right rectus incision. About 200 c.c. of cloudy fluid were present, and this was aspirated and culture was taken. Examination of the sigmoid showed a perforation at the antimesenteric border about 6 inches from the rectosigmoid junction. This perforation was about 1¼ by 1½ cm. in size. The perforation was closed by three layers of sutures. No perforation was evident in the pyloric area. The abdomen was then closed without drainage.

Postoperatively, the patient received plasma and intravenous sodium sulfathiazole. A Levin tube was passed and connected to a suction apparatus. The patient's condition became progressively worse, and he died the day following the operation.

CASE 3.—J. V., a man, aged 55 years, was admitted Feb. 19, 1939, with a chief complaint of severe colicky abdominal pain. The patient had given himself an enema in the morning of the day of admission and immediately afterward experi-

enced the pain. The enema had been given because of constipation of one week's duration. The pain was made worse by body or abdominal movements. Vomiting occurred subsequently.

Previous to admission, he was being treated for carcinoma of the hard palate.

Eyes, ears, and nose were essentially negative. There was an ulcerated area on the hard palate; remainder of the mouth and throat were negative. There were several hard, small lymph glands in the left side of the neck. The heart and lungs were essentially normal. There was a boardlike rigidity of the abdominal muscles with tenderness and rebound tenderness throughout the abdomen. Liver dullness was not decreased. There was no distention. Rectal examination revealed only a moderately enlarged prostate.

The laboratory work-up was negative except for a trace of albumin in the urine and an increase in the polymorphonuclear leucocytes with a shift to the left. X-ray showed free air in the peritoneal cavity. The patient was operated upon about eleven hours after the enema was given, under a diagnosis of perforation of the sigmoid.

The abdomen was entered through a subumbilical left paramedian incision. A large amount of soapy, cloudy fluid was suctioned from the abdomen. The sigmoid was isolated, and a longitudinal perforation about 1 cm. long was found. This perforation was closed with two rows of sutures. Two drains were inserted into the abdomen; one into the cul-de-sac, and one to the left lateral wall. The abdomen was then closed in layers around the drains.

Postoperatively, the patient had a moderate temperature elevation for three days. On the fourth day, the temperature rose to 104°F., and there was moderate distention of the abdomen. This subsided by the fifth day, and from then on the temperature was only slightly elevated or normal. The abdominal wound became infected but healed slowly and steadily and was almost entirely closed at the time of discharge to the clinic for follow-up care on March 27, 1939.

DISCUSSION

In presenting these cases, it is our purpose to call attention again to the inherent dangers of perforation from mechanical manipulation in the relatively insensitive rectum and rectosigmoid even from the trauma of an enema. The avoidance of similar mishaps or at least an appreciable reduction in their incidence requires constant thought to the danger of perforation.

There is no instance in the American literature of a report by a man who is himself responsible for the accident,[10-14] although numerous reports of accidental perforation have been made.[8, 10, 14, 22, 23, 30, 32] Crohn and Rosenak[10] have collected twenty-one cases of perforations by the sigmoidoscope by questionnaires directed to twenty-seven recognized proctologists and gastroenterologists in the United States. Of these perforations, five were produced by specialists, seven by assistants, five were seen in consultation after perforation had occurred, and no data are available concerning the remaining four cases.

Foreign literature abounds with reports of rectal injuries due to enemas and sigmoidoscopy (Ballon and Goldbloom,[3] Pinnock,[22] Gailbraith,[12] Rayer[24] and many others) while in this country, Goldman,[13] Smiley,[27] Brumbaugh,[8] and others have reported similar cases.

Behrend and Herman[5] in discussing their case of sigmoid perforation produced by enema, expressed the opinion that the perforation was produced by the enema tip rather than by the forcible distention of the injection fluid because of the incised character of the perforation rather than a ragged tear. However, this seems unlikely since an enema tip is never introduced above the anal canal. It is difficult to explain a lesion above the peritoneal reflexion produced by the common short rectal tip, and we may assume that the force of the injected fluid probably does play some part, if not the main part, in producing the tear.

Rectal injuries may be caused by a number of factors which vary from trifling damage to rupture with fatal consequences. Among the causes of rectal injuries resulting in perforation are the following:

1. Sigmoidoscope[8, 10, 13, 18, 19, 25, 27]
2. Enema tips, syringes, nozzles, high colonic tubes[3, 5, 12, 22, 24]
3. Thermometers[2, 19, 21]
4. Bougies and rectal dilators[2, 19, 21]
5. Electrodes for fulguration of polyps[10, 19]
6. Spontaneous rupture[16, 28]
7. Urethral sounds making false passage[21]
8. Colpotomy[21]
9. Gunshot wounds[4, 20]
10. Impalement[14, 15, 23]
11. Fracture of pelvic bones[21]
12. Misguided attempts at abortion[11]
13. Accidents in industries or practical jokes[1, 6, 7, 9, 23]
14. Transurethral operations[26]
15. Hydrostatic pressure (water hose)[29]
16. Sadism or sexual perversion[17, 19, 21]
17. Sodomy[21, 30]

In Case 3, while the general impression after careful study of all the history was perforation of acute diverticulitis of the sigmoid, we had not considered the possibility of perforation of the sigmoid from an enema. The history at that time passed over lightly the fact that the patient had himself administered an enema of soapsuds just before the acute onset of his abdominal pain. But subsequent questioning elicited the history of the onset of pain immediately after he had taken this enema, with steady progress in the symptoms, thereafter, till his admission and operation. Fortunately, in his case, a low left paramedian incision afforded satisfactory approach to the lesion with a minimum exposure for the closure of the perforation, contributing much to his recovery.

The fact that in this case there was no severe peritonitis evident at laparotomy when the abdomen was filled with soapsuds from the enema administered by the patient himself with a simple household rubber rectal tip excited our interest in the possibility that the soapsuds may

have reduced the volume of infection when the contaminated fluid entered the peritoneum. At any rate, in this case, there was no generalized peritonitis found at operation eleven hours after the perforation had occurred, and the postoperative course was remarkably free of any clinical evidence of postoperative peritonitis.

When perforation, whatever its cause, has occurred, we are faced with an impending catastrophe unless we move with speed and accuracy. Crohn and Rosenak[10] report a mortality of 47 per cent if operation is done within seven hours, and a mortality of 100 per cent if done from seven to seventy-two hours after perforation. Delayed diagnosis and, therefore, delayed operation results in generalized septic peritonitis with its inevitable high mortality.

While perforation is more likely to occur in cases presenting weakening of the intestinal wall by malignancy, diverticulum, ulceration, or colitis, many cases have been reported without essential pathology of the bowel. With such common use of high colonic irrigation, it is surprising that the incidence of perforation is not higher. Attention is again called to the indiscriminate use of the sigmoidoscope. Proper training in its use with constant attention to the details of its use, knowledge of anatomy of the area, sufficient lubrication, gentle handling without force or undue pushing, always with removal of the obturator after the instrument has entered the anal canal, with proper lighting to visualize the direction of the intestinal canal are safeguards for the prevention of accidents. Of utmost importance is a complete history as to previous operations or pelvic disease that might have given rise to obstructive bands or adhesions involving the rectosigmoid, preventing passage of the sigmoidoscope. Important also is a thorough preliminary examination of the patient who may present large pelvic tumors that preclude the use of the sigmoidoscope by their encrouchment on the rectosigmoid. Particular care should also be used when the history reveals passage of blood by stool because this may indicate a weakened intestinal wall from tumor, colitis, diverticulitis, etc.

SUMMARY

Three cases have been presented of traumatic perforation of the rectosigmoid; one the result of intrarectal biopsy following sigmoidoscopy, one produced by a colonic irrigation, and the third by an enema. In all cases, the intestinal wall was normal and the perforation was purely traumatic. Sigmoidoscopy, even in highly trained hands, is not without danger. Other mechanical manipulations in this region are fraught with danger. Even a simple colonic irrigation or enema may result in perforation of the rectosigmoid or bowel. The fact that simple enema or colonic irrigation itself may result in perforation is to be considered in differential diagnosis of the acute abdomen.

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REGIONAL ENTERITIS OF THE PROXIMAL JEJUNUM FOLLOWING TRAUMA

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THE clinicopathologic syndrome of terminal ileitis was brought to the attention of the medical profession in 1932.[1] Since then our concepts of the disease have changed greatly, as evidenced by the changes in terminology, namely: regional enteritis, regional enterocolitis, regional cicatrizing enteritis, granulomatous jejuno-ileitis. These changes in terminology bespeak the variations in opinion about the anatomic location of this lesion.

The most common site involved is still the terminal ileum (Table I). Of 200 cases reported by Crohn and Yunich,[2] only seventeen were diffuse or involved higher portions of the ileojejunum. Of their forty-three cases, Warren and Miller[3] found twenty-seven with involvement of the terminal ileum, ten with involvement of the cecum, and two with involvement of other areas of the small bowel. Sussman and Wachtel[4] state that 60 per cent of their twenty-three cases affected the terminal ileum, and although they referred to the occurrence of localized jejunitis, none is reported in their series. Bockus,[5] in a series of twenty-one cases, found none involveing the jejunum. Brown and Donald,[6] reporting on the experiences at the Mayo Clinic, found only 5 of 178 cases of enteritis primarily involving the jejunum. While Browne and McHardy,[7] in a comprehensive review of over 1,000,000 hospital admissions and 7,970 autopsies, found only one case of enteritis involving the jejunum. Ravdin and Johnston,[8] in a review of the literature in 1939, tabulated 462 cases of regional enteritis, of which only sixteen involved the jejunum. Harris and co-workers[9] were among the first to report a case of cicatrizing enteritis wholly confined to the jejunum. The first constriction in this case began, however, about 60 cm. below the ligament of Treitz. Several single cases involving the jejunum are found in the more recent literature.[10-12] In none of these is the lesion confined to the most proximal portion of the jejunum. In Johnson's case,[11] the first stenotic area was about three inches below the ligament of Treitz, and skip areas involved about forty inches of small bowel. In Brewster's[12] case, the first area of constriction was about two and one-half feet below the ligament of Treitz.

The case reported here is of interest, not only because of the confinement of the pathology to the most proximal portion of the jejunum, but also because of the preceding trauma which may have an etiologic relationship in the pathogenesis of the lesion.

Received for publication, Oct. 27, 1944.

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TABLE I

FREQUENCY OF INVOLVEMENT OF JEJUNUM IN REPORTED CASES OF REGIONAL ENTERITIS

AUTHOR	TOTAL NUMBER OF CASES	NUMBER INVOLVING ILEOJEJUNUM	JEJUNUM
Crohn and Yunich	200	17	
Warren and Miller	43	2	
Boekus	21	0	0
Ravdin and Johnston	462		16
Brown and Donald	178		5

CASE REPORT

A 23-year-old soldier was hospitalized July 3, 1943, for injuries sustained that day when the motorcycle which he was driving ran into the rear end of a truck, the motorcycle driving on under the body of the truck. The exact manner in which the injuries were sustained could not be determined because the patient was asleep at the time of the collision and was unconscious for a short time afterwards. He sustained multiple lacerations and abrasions of the face, mainly the forehead and left cheek, and a depressed, compound fracture of the left maxilla and zygoma, as well as a fracture of the fifth rib. His principal complaint was severe, generalized abdominal pain which apparently was not cramplike.

On examination the abdomen did not appear distended and there was no visible sign of abdominal wall contusion. There was generalized abdominal tenderness, but this seemed more somatic than visceral. Peristalsis was audible. Flat plate of the abdomen was taken and no free air in the peritoneal cavity was seen.

The abdominal pain subsided within nine days. During this period the patient continued to pass flatus and have bowel movements, but vomited only a few times. The facial fracture required extensive surgical interference. There were no symptoms referable to the abdomen until the end of August, or about seven weeks after the accident, when for three days he became constipated and suffered malaise and abdominal discomfort; all of these symptoms were for the most part relieved by an enema and a saline cathartic. However, there remained some residual and abdominal soreness. In spite of some apprehension about the condition of his abdomen since the accident, the patient ate well throughout the attack, did not vomit, and eventually resumed normal bowel habits.

Physical examination at this time revealed mild abdominal tenderness with slight accentuation in the left upper quadrant but, with continued tenderness over the fractured left rib. This was thought to be of little significance. His symptoms having subsided, he was given a furlough for thirty days.

Upon his return from furlough, the patient stated that he had become much worse. Vomiting occurred after nearly every meal. This was accompanied by abdominal pain which was said to be generalized. Only light and liquid foods were taken but the vomiting continued. In spite of this, his bowel habits remained normal.

Physical findings still remianed equivocal, with abdominal tenderness diffuse and no distention being present. The temperature remained normal. There was no leucocytosis. The sedimentation rate was 6 mm. per hour. Stool cultures were negative for pathogenic microorganisms.

Roentgenographic examination of the gastrointestinal tract, following a barium sulfate meal, showed the stomach and duodenum to be dilated, the duodenum to a marked degree. The opaque medium was almost completely arrested at the level of the ligament of Treitz. Distal to this part for about twelve inches, the jejunum

showed a complete loss of mucosal markings, marked stenosis, and absence of peristaltic waves. During fluoroscopic examination it was noted that this portion of the bowel was rigid and nondistensible (Figs. 1 and 2). While there was a scattering of barium in the rest of the small bowel, no further organic constriction was demonstrated. Study of the involved portion of the bowel with the Miller-Abbott tube yielded no additional information.

With this evidence, a diagnosis of stenosing obstructive lesion of the proximal jejunum was made and the patient prepared for operation by continuous Wangensteen suction and parenteral fluids. The symptoms of obstruction became prominent before the operation, but no mass could be palpated abdominally, and no visible peristalsis was detected.

Fig. 1.

Fig. 2.

Fig. 1.—Roentgenogram of stomach, duodenum, and proximal jejunum one hour after administration of a barium sulfate meal, showing gastric and duodenal dilatation as well as the stiffness, loss of mucosal markings, and constrictions of jejunum.

Fig. 2.—Four hours after the administration of barium sulfate, showing that very little of the meal has left the stomach. The involved portion of jejunum is well outlined.

Oct. 14, 1943, an exploratory laparotomy was performed under general anesthesia. The findings were surprising. The most proximal twelve inches of the jejunum, beginning at the ligament of Treitz, were bright in color, appeared indurated and edematous, and could be likened to a piece of garden hose in consistency. The mesentery, too, was markedly edematous and contained numerous enlarged glands. In fact, glands were palpable and visible throughout the entire mesentery of the small intestine, decreasing in size caudally. The appearance of the involved bowel and mesentery was not unlike that of a subacute, nonspecific, regional enteritis. It was obvious that this was the cause of the obstruction. The stomach itself was dilated, but otherwise appeared normal. Because of the acuteness of the process, and because of its extension into the duodenum, it was decided not to remove the bowel at this time but rather to do a short circuiting operation and put the involved portion of the bowel at rest. Accordingly, a posterior gastrojejunostomy was effected, leaving a loop of jejunum of approximately twenty-two inches. One of the regional mesenteric glands was removed for biopsy.

The biopsied lymph node showed a marked increase of plasma cells and some polymorphonuclear leucocytes. The endothelial cells appeared swollen. The pathologist called this a subacute lymphadenitis, and stated that the findings were not inconsistent with a diagnosis of regional enteritis.

Postoperative convalescence was without incident and the patient was up and about the ward within two weeks, tolerating a diet low in roughage but high in calories and vitamins. He was free of obstructive symptoms. However, it was necessary to maintain him on a low residue diet, as roughage seemed to produce some abdominal discomfort and occasional vomiting. The patient was observed for about five months, during the latter portion of which time he complained of inability to eat a large meal and stated that for one or two hours after nearly every meal he had some cramplike pains in the epigastrium, following which period the pains subsided and he was again comfortable. It began to affect his food intake, for because of the pain he purposely omitted meals. However, his general condition was not affected and although his former weight was not regained, he maintained his current weight. After a barium sulfate meal, x-ray examination of the upper gastrointestinal tract was done and it was noted that while the gastroenterostomy stoma was functioning well, some barium passed through the pylorus into the duodenum where it was literally churned, and then regurgitated into the stomach from where it entered into the jejunum through the enterostomy. The duodenum was markedly dilated and the deformity and obstructive lesions in the jejunum were still evident.

The patient was again operated upon,* March 26, 1944, under spinal anesthesia. The acuteness of the inflammatory process had subsided. The proximal portion of the jejunum was no longer red or indurated but appeared shriveled and constricted in areas, and the color was a dull and lustreless pink. The regional glands were still enlarged but the general appearance was that of a chronic process. The duodenum was markedly dilated but otherwise normal. The mesenteric lymphadenitis noted generally at the previous operation had subsided everywhere except in the immediate area attached to the involved jejunum. The gastroenterostomy was taken down and the first twelve inches of the jejunum resected, utilizing an end-to-end anastomosis of the remaining segments.

The postoperative course was again without incident and the patient was again up and about the ward within two weeks. Following a suitable time in which foods were introduced gradually, an unqualified full diet was prescribed and taken without difficulty, the patient was sent on a thirty-day furlough from which he returned about fifteen pounds heavier and in excellent general health and spirits. At that time he had no complaints.

Gastrointestinal roentgenogram two months after the last operation showed that the duodenum had returned to almost normal size and the motility was normal. Gastroscopic examination revealed the remains of a scar at the site of the old gastroenterostomy.

The specimen removed consisted of the first 40 cm. of jejunum (Fig. 3). The proximal 3 cm. were dilated but showed an absence of the plicae circulares. Following this there was a constricted area followed by another dilated area in which the plicae circulares were absent. In all there were three areas of constriction, and in about 12 cm. the plicae circulares were absent. Dilated blood vessels were seen in the serosa and the mesenteric lymph nodes were enlarged. Microscopically the stenotic areas showed a loss of normal architecture of the mucosal glands and in some areas there was a complete loss of the epithelial element, in which case they were replaced by neutrophiles and round cells. The entire submucosa was markedly thickened and contained large aggregates of plasma cells, small round cells, and scattered

*This operation was performed by Dr. Alton Ochsner.

eosinophiles. An occasional giant cell was present in the submucosa. The muscle layers were distorted and the serosa was markedly thickened, edematous, and contained dilated blood vessels. In the areas where the villi were intact and no gross lesions of the mucosa were seen, infiltration of plasma and round cells about the glands was evident. The submucosa consisted of a dense, highly vascularized connective tissue. The pathologic diagnosis was regional enteritis.

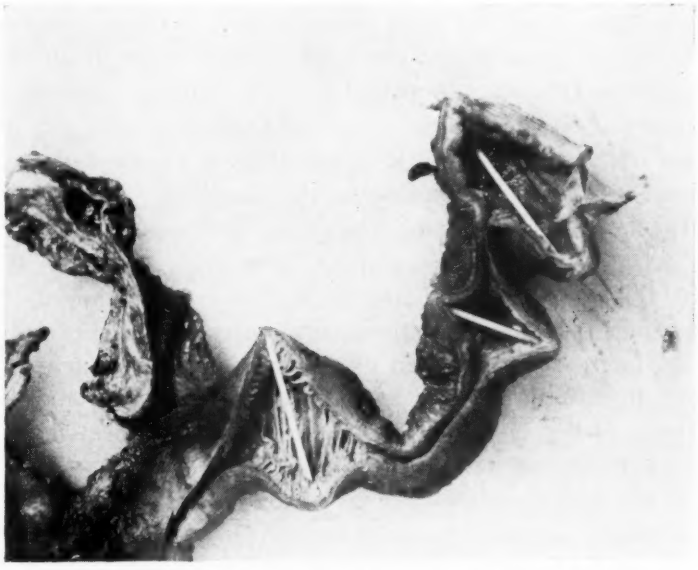

Fig. 3.—Photograph of resected portion of jejunum and attached mesentery, showing dilatations and constrictions and loss of plicae circulares.

DISCUSSION

Etiology.—Much has been written, but little is known, about the etiology of regional enteritis. Because of the microscopic features simulating a low-grade inflammatory process or granuloma, tuberculosis was thought of as a possible etiologic agent. Exhaustive investigation yielded no evidence that the tubercle bacillus is the cause of this type of enteritis,[8, 13] although a true tuberculous enteritis may masquerade as a regional enteritis. Outstanding among other organisms incriminated are those of the Shigella group. Felsen[14] has claimed an etiologic relationship between the Shigella organisms and regional enteritis, as well as ulcerative colitis, on the basis of epidemiologic, bacteriologic, and serologic studies. This viewpoint has not gained widespread acceptance and most workers in the field deny that a specific bacterial agent has been demonstrated to be the cause of this disease. Ravdin and Johnston,[8] in their comprehensive review, refer to no less than twelve possible etiologic factors: (1) bacteria, (2) bacterial toxins, (3) viruses, (4) protozoa, (5) metazoa, (6) achylia gastrica, (7) allergy, (8) foreign bodies, (9) nonspecific inflammation of appendix, (10) impairment of blood supply, (11) interference with lymphatic supply, and (12) trauma.

Trauma is an etiologic factor about which varying opinions have been expressed. Crohn[13] denies that there is a cause and effect relationship between trauma and regional enteritis, and where the history of preceding trauma is obtained, the latter may be an unrelated coincidence, or at most an aggravating factor. Contrary to this is a report by Reichert and Mathes[15] of a 40-year-old man who developed cramplike abdominal pain, associated with vomiting and diarrhea, two weeks after a severe blow to the abdomen from the steering wheel of an automobile. The symptoms gradually increased and two months later an operation was required. Upon exploration of the peritoneal cavity, a portion of the ileum which was apparently traumatized at the time of the accident was found kinked and bound down by adhesions. The mesentery was short, thick, and boggy, and contained dark-colored material at its roots. No glandular involvement was described. Because of enlargement of the lacteals, lymphatic obstruction was advanced as an important etiologic factor. In experimental animals, Reichert and Mathes[15] succeeded in producing cicatrizing contractions of various parts of the bowels by injecting sclerosing agents into the subserosal and mesenteric lymphatics. Bell,[16] however, was unable to produce cicatrizing enteritis or any lesion simulating the condition by interfering with the blood supply to the intestinal tract.

Traumatizing surgical procedures and intestinal trauma from intrinsic causes have been incriminated as possible causes of granulomatous intestinal lesions. Leonardo[17] described a case of ileocecal granuloma developing only eleven days after a very difficult appendectomy, necessitating much traumatization. In 1928, before regional enteritis was established as a disease entity, Ginsburg and Klein[18] reported three cases of stenotic lesions of the small bowel, developing two weeks to five months after the relief of strangulated inguinal hernia. The thought is expressed that interference with blood supply, insufficient to cause gangrene, may result in enough devitalization of tissue to produce cicatricial changes. Two types of lesions are described, an anular type and a tubular type. In another paper, Ginsburg and Oppenheimer[19] point out that "nonspecific granulomas of the intestine" may form secondary to sealed perforation and secondary to known vascular disturbance of the gut. In a paper on "Ineffective Granuloma," Mock[20] discusses various factors that may encourage the formation of chronic granuloma of the intestines. He discusses surgical trauma at great length. He refers to granulomas developing about silk sutures and those forming around ligatures of omentum or mesentery as well as around foreign bodies left in the peritoneal cavity. In regard to extraneous injuries he says, "The importance of trauma in the forming of these obscure intra-abdominal tumor masses, so often mistaken for malignant tumors, has never been sufficiently stressed. No case of granuloma as the direct result of an accident, such as from an automobile or a fall, has ever been reported, I believe."

In our case the trauma is a challenging factor in the production of the final lesion. While a definite cause and effect relationship cannot be established, there are many features which favor such a possibility. The patient had no symptoms whatever before the accident, yet the disease progressed rapidly to a stenosis once the symptoms became manifest. The portion of the gut involved is one that would be more subject to external trauma because of its relatively fixed anatomic position. The limitation of the lesion to a small segment of terminal ileum is not uncommon. However, when the lesion involves more proximal portions of gut, skip areas occur with great regularity. In our case the pathologic process remained limited to the jejunum throughout the five months' interval between the two surgical procedures.

On the other hand, it is difficult to conceive how trauma by itself can produce a lesion that is essentially inflammatory in character. The usual type of traumatic injury of the hollow viscera is a perforation. Kelly,[21] in discussing nonpenetrating abdominal injuries, found that intestinal perforation occurred in all of his cases of severe injury. Another method by which severe injury to the gut could be produced through trauma is from hemorrhage or other vascular damage. However, in this case, no evidence of extensive hemorrhage was seen at operation or could be presumed clinically. In the case reported by Reichert and Mathes,[15] the finding of dark-colored material at the root of the mesentery was suggestive of old hemorrhage. The lapse of nearly two months between the injury and the development of symptoms is also surprising. Finally, in this mechanical age when abdominal trauma is common, it would be suspected that such cases as ours will be reported in the literature with greater frequency.

One case, however, that bears some resemblance to ours is that described by Pupini,[22] in which a 36-year-old man sustained an injury to the abdomen by falling against the steering wheel of a launch. In this case symptoms occurred immediately and continued without remission until he was admitted to the hospital two months later. The symptoms were those of intestinal obstruction. Upon exploration, about 10 cm. of mid-ileum were found involved. Gross appearance of the bowel was similar to the appearance of the jejunum in our case at the first operation. No glandular involvement is mentioned and no microscopic description is given. In the case of regional jejunitis reported by Browne and McHardy,[7] a history of severe abdominal trauma was elicited. Severe symptoms in their case occurred seven days after the abdominal trauma. The lesion involved the mid-portion of the jejunum which appeared thickened and "acutely inflamed." Microscopically, the bowel wall showed acute exudative and chronic inflammatory changes. There is no mention of enlarged mesenteric lymph nodes.

Symptomatically, the case reported presents the unusual but rational sequence that one would expect in inflammatory and stenosing lesions at the proximal end of the small intestine. There is less emphasis upon

disturbance of bowel function as represented by diarrhea and constipation, more upon upper abdominal distress and vomiting closely simulating the picture of pyloric obstruction.

Even though the inflammatory lesions subsided after the first operation, the patient continued to have mild symptoms, apparently because of the mechanical difficulties in the dilated loop of the duodenum. In spite of the functioning gastroenterostomy stoma, some material entered the blind loop of duodenum. The patient became practically asymptomatic after resection of the involved loop of the jejunum.

SUMMARY AND CONCLUSIONS

1. A case of regional enteritis confined to the proximal jejunum is presented.

2. The symptoms began about two months after a nonpenetrating injury to the abdomen.

3. The possible etiologic relationship of trauma to regional enteritis is discussed.

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INTRAPERITONEAL ABSORPTION PATTERNS OF SULFONAMIDE DRUGS (WITH SPECIAL REFERENCE TO MICROCRYSTALLINE SULFATHIAZOLE) AND A COMPARISON OF COINCIDENT CONCENTRATIONS IN THE PORTAL VEIN, SYSTEMIC CIRCULATION, AND PERITONEAL FLUID

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THE purposes of this paper are: (1) to demonstrate the absorption curves of sulfonamide drugs, with special reference to microcrystalline sulfathiazole,* in the normal peritoneal cavity and (2) to compare the concentrations of these drugs in the portal and systemic veins and in the free peritoneal fluid.

Increasing attention has been given to the administration intraperitoneally of sulfonamide drugs of greater antibacterial potency than sulfanilamide.[1, 2, 3, 6, 7, 9, 11, 17, 20, 21, 24] However, the lower solubilities and certain other differences in physical properties of such compounds, especially sulfathiazole and sulfadiazine, make the commonly used method of sprinkling the crystalline material into the peritoneal cavity even more objectionable than when sulfanilamide is so introduced. Microcrystalline sulfonamides[2] would appear to offer means of obtaining more complete dispersion of the sulfonamide in the abdomen and of avoiding, to some extent at least, the foreign body reaction caused by caking and clumping of the material when introduced by sprinkling. Furthermore, when employed in the finely divided state of microcrystals, solution of the sulfonamide occurs much more rapidly because of the much larger surfaces exposed to the solvent action of the body fluids so that higher concentrations are obtained. Favorable results have been reported by Ferguson[7] and by Chambers, Harris, Schumann, and Ferguson[2] when microcrystalline sulfathiazole was employed locally for therapeusis in a variety of conditions. The latter have also described the response of rabbits and dogs to intraperitoneal administration of sulfathiazole in the form of microcrystals.

Experiments described in this paper were designed to provide additional information concerning the behavior of microcrystalline sulfathiazole introduced into the abdomen of the dog. The influence of the method of administration, whether as powder or suspension, also has

Received for publication, July 3, 1944.

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been investigated. The rate of absorption of sulfathiazole from the peritoneum was studied by means of serial determinations of its concentration in the peripheral blood. However, the possibility that this does not provide an adequate measurement must be considered, and statements to this effect have been made,[5] a marked uptake of drug by the liver with resulting injurious effects having been postulated. One of us has pointed out[15] that the evidence did not warrant the inferences based thereon. Examination of the portal blood was included in our studies to make certain that microcrystalline sulfathiazole might not differ in this respect from ordinary sulfathiazole. Peritoneal fluid also has been examined when present.

TECHNIQUE

Sulfonamide drugs, 0.28 Gm. per kilogram of body weight, were administered into the peritoneal cavities of normal dogs. Microcrystalline sulfathiazole suspension (20 per cent in gelatin) was given through an 18 gauge needle inserted through the abdominal wall; no anesthesia was necessary. Approximately two minutes were required to empty the syringe. In order to avoid complications caused by caking, which often occurs when sulfonamide drugs are dusted into the peritoneum, microcrystalline sulfathiazole powder, sulfathiazole powder, and sulfanilamide powder were insufflated with a Shelanski vaginal insufflator through a 1 cm. incision, using an open technique for incising the peritoneum developed by one of us for peritoneoscopy.[16] Sodium pentothal anesthesia was used. At stated intervals, blood was taken by venipuncture. Plasma was used for sulfathiazole determinations, and whole blood for sulfanilamide. At approximately the time that maximum systemic sulfonamide levels were expected, the animals were anesthetized by intravenous nembutal, 0.33 to 0.44 Gm. per kilogram, and subjected to laparotomy. Peritoneal fluid was aspirated, after which blood was withdrawn from the portal vein and from the heart. Liver biopsy was then performed. The incisions were closed in layers. Additional venipunctures were performed postoperatively. Peritoneal fluid was filtered before it was analyzed.

RESULTS

Insufflation of sulfanilamide into the peritoneal cavity (Fig. 1) caused a rise in blood sulfanilamide, more rapid than that described by Jackson and Coller[12] following implantation of sulfanilamide in peritoneal cavities of dogs but similar in other respects. Lower values were obtained by Keeley.[13] Ambrose and Haag[1] used only 0.1 Gm. per kilogram and their results thus cannot be compared directly with ours.

Insufflation of sulfathiazole in its ordinary crystalline form led to peak values two to three hours after administration of the drug, distinctly later than those obtained after sulfanilamide (Fig. 2). The

graphs obtained by plotting concentration in plasma against time resemble those shown for whole blood by Ambrose and Haag,[1] differences in height of the rise being explained in part by the higher dosage employed in our experiments, and in part by the difference between plasma

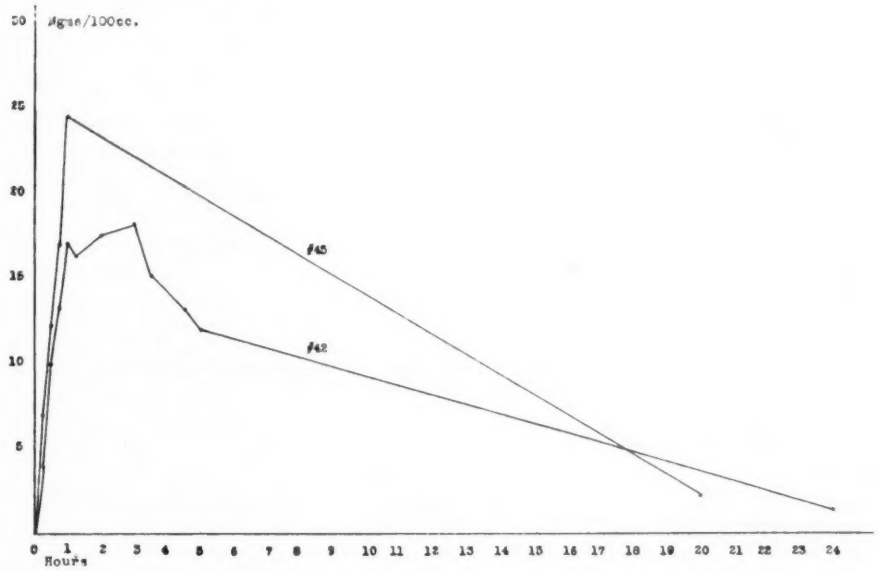


Fig. 1.—Blood sulfanilamide concentration after intraperitoneal insufflation of sulfanilamide.

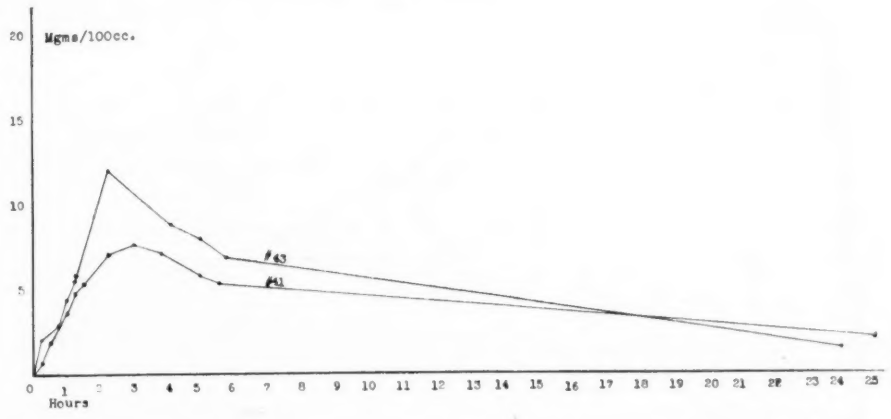


Fig. 2.—Plasma sulfathiazole concentration after intraperitoneal insufflation of sulfathiazole powder.

and whole blood sulfathiazole concentrations. (Plasma sulfathiazole concentrations are ordinarily about 25 to 35 per cent higher than corresponding concentrations in whole blood.)

Insufflation of microcrystalline sulfathiazole caused a rise to an average of about 12 mg. per 100 c.c. in plasma. No marked difference in plasma sulfathiazole concentrations is evident (Fig. 3) as compared with

the response to ordinary crystals of sulfathiazole. There is some indication that the curves for the latter may be lower, although it is impossible to draw conclusions from two experiments.

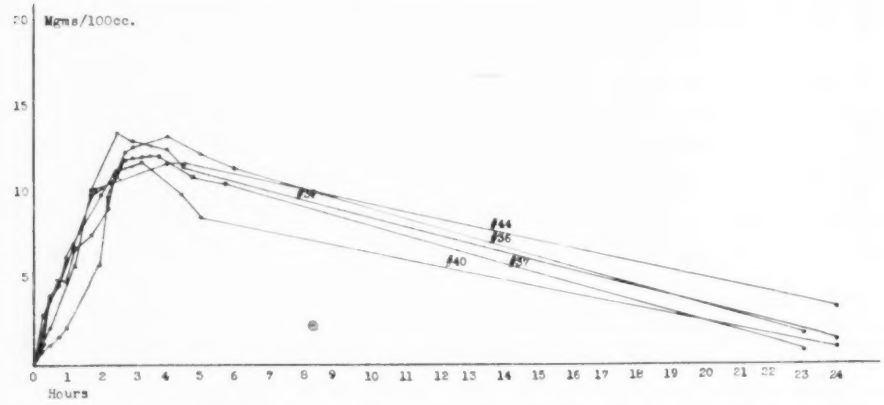
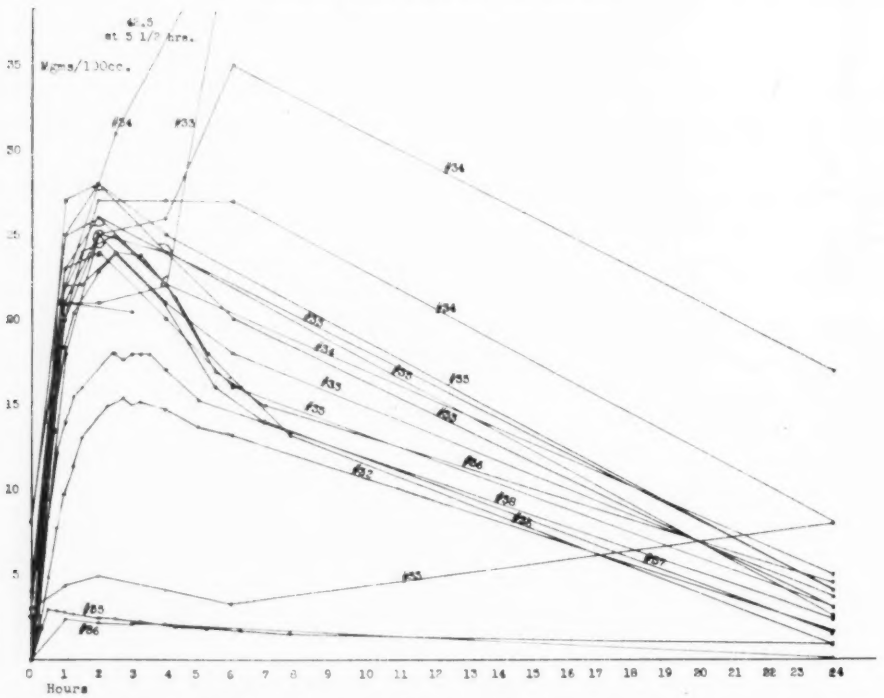


Fig. 3.—Plasma sulfathiazole concentration after intraperitoneal insufflation of microcrystalline sulfathiazole powder.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mg. per 100 c.c. was observed, at two hours this had risen to 20.7, at four hours it was 18.9, and at six hours it was 18.6 (Fig. 5). Our results confirm those of Chambers, Harris, Schumann, and Ferguson.[2] Gilchrist and his associates[9] found even higher values but used larger doses.

The results of three experiments differed from the remaining seventeen in that only slight increases occurred in plasma drug concentration after intraperitoneal administrations of sulfathiazole microcrystal suspension. The technique employed in making the injections, it is believed, precluded the possibility of piercing a viscus, and the high level found twenty-four hours after the injection in Dog 33 eliminates

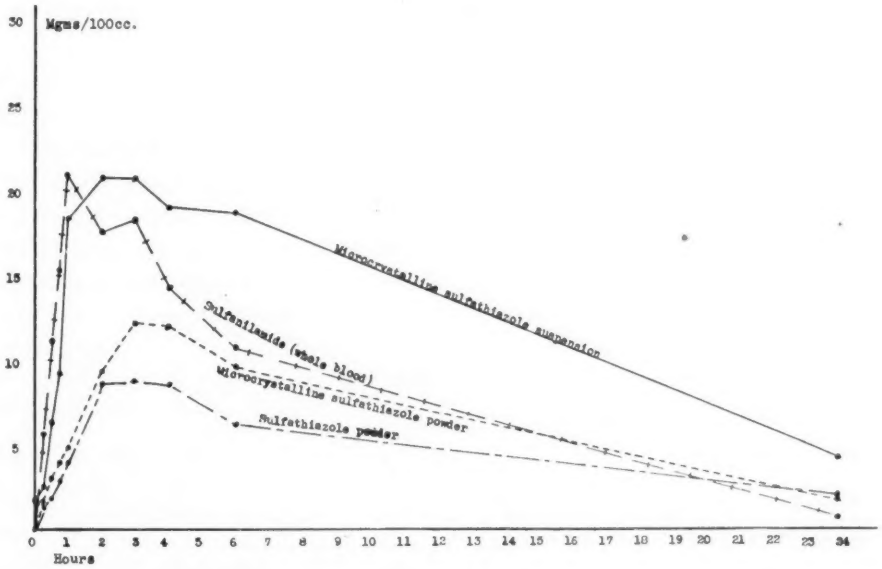

Fig. 5.—Mean plasma sulfonamide concentration after intraperitoneal implantation of sulfonamide drugs.

such an explanation. Furthermore, laparotomy done on Dog 32 in the course of another experiment in which the rise in drug concentration in plasma was less than 1 mg. per 100 c.c. showed the drug to be present in the peritoneal cavity in the form of globules 1 to 2 mm. in diameter. In this state a relatively small surface would be exposed to the solvent action of peritoneal fluid and absorption might be delayed.

In two experiments after an initial rise, followed by a period of several hours characterized by comparatively stable concentrations, a marked secondary rise in plasma sulfathiazole occurred. This again might be caused by increased dispersion of the suspension of microcrystals. Another possible explanation is an increase in solution of the sulfathiazole following stimulation of the formation of peritoneal fluid by the drug. Because of the low solubility of these substances, the volume of fluid available together with its protein content will be one of

the factors limiting the rate of absorption. Protein is important because of the existence of sulfathiazole-protein complex. Also to be considered is the existence of more than one pathway by which transfer from the peritoneal space to the blood stream could occur.

Sulfathiazole concentrations exceeding 35 mg. per 100 c.c. of plasma were observed in three experiments. In each, a similar experiment had been done on the preceding day and some residual sulfathiazole was found in the plasma at the start of the experiment. However, other experiments under similar conditions failed to show exceptionally high levels and in one dog little rise over the residual level occurred after administration of a second dose intraperitoneally.

Fig. 5 shows the mean concentration curves for sulfanilamide, sulfathiazole, microcrystalline sulfathiazole powder, and microcrystalline sulfathiazole suspension.

Table I shows concentrations of sulfonamide drugs in plasma or blood samples collected at the same time from the heart and from the portal vein. In some instances peritoneal fluid was collected and analyzed as well. The drug concentrations in portal and heart blood are the same. The results are in agreement with those of Jackson and Coller who found no differences in sulfanilamide concentrations between portal and peripheral blood four hours after intraperitoneal administration. Maximal differences were observed by them within thirty minutes after the

TABLE I

COMPARISON OF COINCIDENT SULFONAMIDE LEVELS IN THE PORTAL AND SYSTEMIC CIRCULATION AND IN THE PERITONEAL FLUID

DOG NO.	DRUG	PERITONEAL FLUID (MG. PER 100 C.C.)	TIME (MIN.)	PORTAL BLOOD (MG. PER 100 C.C.)	RATIO OF PORTAL BLOOD LEVEL OVER PERITONEAL FLUID LEVEL	TIME (MIN.)	HEART BLOOD (MG. PER 100 C.C.)	RATIO OF HEART BLOOD LEVEL OVER PORTAL BLOOD LEVEL
45	Sulfanilamide powder	106.0 (serosang.)	60	25.6	0.24	70	24.5	0.96
42	Sulfanilamide powder	38.0	180	18.2	0.48	175	18.2	1.00
43	Sulfathiazole powder	27.0 (serosang.)	240	10.0	0.41	253	8.9	0.89
41	Sulfathiazole powder	75.0 (serosang.)	180	8.4	0.11	175	7.7	0.92
44	Microcystalline sulfathiazole powder	49.0 (serosang.)	240	11.9	0.24	240	11.8	0.99
40	Microcrystalline sulfathiazole powder	98.0	150	10.4	0.11	150	11.3	1.09
37	Microcrystalline sulfathiazole suspension	172.0	150	13.0	0.08	150	13.6	1.05
35	Microcrystalline sulfathiazole suspension	Not done	180	20.5	---	180	20.0	0.98
34	Microcrystalline sulfathiazole suspension	No free fluid	350	42.9	---	350	42.5	0.99
33	Microcrystalline sulfathiazole suspension	Not done	360	39.8	---	320	38.2	0.96
	Mean			20.1	0.24		19.7	0.98±0.06

drug was implanted, when the portal blood concentration was 40 per cent higher than that of the peripheral blood, but the concentrations soon approximated those of the peripheral blood. Obviously, comparisons of drug concentrations in portal and peripheral circulation can be evaluated only when distribution through the body is complete and equilibrium between tissues and plasma has been attained.

As is to be expected, high concentrations of sulfathiazole or sulfanilamide drug are present in the peritoneal fluid. The number of specimens is insufficient to evaluate the concentrations in peritoneal fluid established by the several forms of sulfathiazole tested. The highest concentrations, however, are to be seen in the fluids taken after injection of the suspension of microcrystals.

The incidence of vomiting was high in those experiments in which the suspension of sulfathiazole microcrystals was used, occurring in nine of twenty-two experiments. Sulfathiazole administered in comparable dosages in other forms did not cause vomiting.

Small amounts of fluid were found in the peritoneal cavity in nine of eleven experiments. Of these, five showed clear fluid and four showed fluid that was slightly serosanguinous. The serosanguinous fluid in each instance was found in those experiments in which incisions had been made for insufflation.

DISCUSSION

The rate of absorption of sulfonamide compounds from the peritoneal cavity depends on many factors: the chemical nature of the compound used, its physical state, the method of administration, the extent of binding by protein, specific differences in permeability, and the state of the peritoneum. It appears that plasma levels, in turn, depend on the ease of absorption, the availability of the drug for excretion, and the extent of tubular reabsorption in the kidney. In this study of intraperitoneal administration it is shown that crystal size as well as the use of a suspension, as compared with insufflation, greatly influences the rate at which sulfathiazole enters the blood. Similar differences between sulfathiazole administered as a powder and as a suspension were observed by Crutcher, Daniel, and Billings.[3]

A noteworthy feature of the experiments dealing with intraperitoneal injection of a suspension of sulfathiazole microcrystals is the high concentrations of this drug that are established in the plasma. At a given dosage rate, sulfathiazole administered orally fails to reach levels as high as those characteristic of sulfanilamide, sulfapyridine, sulfadiazine, or sulfamerazine, mainly due to the fact that it is so readily excreted. Thus, the average concentration of 20 mg. per 100 c.c. maintained for several hours exceeds any that can be obtained by other means save continuous intravenous administration of the sodium salt. Multiple subcutaneous injections of saline suspensions of sulfathiazole by Poth and Fernandez[17] gave comparable concentrations but only with much larger amounts of drug. The frequency with which vomiting occurred

at such high levels, however, suggests that somewhat smaller amounts be employed by this route. Despite the variable response to single injections, our experience with repeated intraperitoneal injections, although limited, points to this as a promising procedure enabling maintenance and a degree of control of blood sulfonamide levels.

It has already been pointed out by one of us (Pearce[15]) that apprehensions concerning excessively high concentrations of sulfanilamide in the portal blood following intraperitoneal administration were not warranted. Our experiments demonstrate that sulfathiazole, like sulfanilamide (Jackson and Coller[12]), showed no significant differences between drug concentrations in portal and systemic circulation within one hour after the drug was given. Differences such as those observed by Jackson and Coller[12] occurred only for a comparatively short time after the drug was administered. Rapid transfer of the drug from peripheral blood to tissues before the concentration in the latter reaches the point of equilibrium could explain these initial differences. Thus, it is unnecessary to postulate a selective absorption by the liver. We observed no physical evidences of hepatitis despite some high plasma sulfathiazole concentrations obtained with the microcrystalline suspension. Judgment must be reserved, however, until a detailed histologic study of liver biopsies has been completed.

Differences in rate and extent of absorption of these drugs are to be anticipated in the presence of the pathologic peritoneum. Inflammatory processes, where free peritoneal fluid is found and the peritoneal surfaces become edematous, tend to decrease absorption from the serous surfaces, although in the initial phase of peritonitis, when simple capillary hyperemia alone is present, absorption may be increased. When well-organized barriers such as abscesses are formed, peritoneal absorption may be slowed and high local drug concentrations may remain for long periods as shown by clinical observations of protracted blood levels. Rates of absorption shown in the present experiments, therefore, are more rapid than those encountered in disease involving the peritoneum.

High local concentrations of sulfonamides have a greater bacteriostatic effect than low concentrations of the drugs. According to Mueller and Thompson[14] more organisms may be affected and the drug action becomes bactericidal. Evidence from many sources[4, 8, 10, 12, 14, 18, 19, 22, 23] testifies to the value of sulfanilamide implanted in the peritoneal cavity. However, Epps, Ley, and Howard,[6] Stafford,[21] and Poth and Fernandez[17] found sulfathiazole to be more effective in peritonitis than were other sulfonamide drugs. The latter found that a combination of high blood concentrations maintained together with high local concentrations is the best response. Whether sulfathiazole is the drug of choice for such a purpose requires additional study, since despite its high antibacterial activity the greater rapidity with which it is excreted and the possibility of complications in the urinary tract and other toxic manifestations may

make sulfadiazine or sulfamerazine preferable. Sulfadiazine is available in microcrystalline form and has been studied after being implanted into the peritoneal cavity at operation by Hawking and Hunt.[11] Absorption was incomplete and sulfadiazine lumps surrounded by adhesions and lymph were found at necropsy ten days postoperatively. Presumably, use of a suspension of microcrystals would obviate this complication. Sulfadiazine powder has been employed intraperitoneally with good results by Ryan, Bauman, and Mulholland[20] and Walter and Cole.[24] However, Crutcher, Daniel, and Billings[3] found a more marked inflammatory reaction caused by sulfadiazine than by sulfanilamide or sulfathiazole. Differences in the chemical and physiologic behavior of the various sulfonamide drugs are sufficiently marked to make obligatory a detailed study of each when employed in a new dosage, form, or route of administration.

Because of the facility with which suspensions of microcrystalline sulfonamide can be injected directly into the peritoneal cavity, application of this form of therapy suggests itself in the treatment of peritonitis and the management of blast injuries. The use of penicillin intraperitoneally also awaits investigation.

SUMMARY

1. Sulfathiazole introduced into the peritoneal cavity of normal dogs in the form of microcrystals was more rapidly absorbed than was crystalline sulfathiazole when compared on the basis of concentrations of drug in the plasma.

2. Microcrystalline sulfathiazole injected into the peritoneum as a suspension gave higher concentrations of drug in blood plasma than did comparable amounts administered by insufflation, although the response to the former was not uniform.

3. High and sustained concentrations of sulfathiazole in plasma can be obtained by intraperitoneal injection of a suspension of microcrystals.

4. Simultaneously collected samples of blood from portal vein and heart contained practically identical concentrations of sulfonamide drugs 60 to 360 minutes after intraperitoneal administration either as crystals or microcrystals.

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AN IMPROVED METHOD FOR THE IMPLANTATION OF SULFONAMIDE COMPOUNDS IN THE ABDOMINAL CAVITY AND LOCAL WOUNDS

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WE ASSEMBLED, in 1943, an apparatus to implant sulfanilamide powder or crystals in the abdominal cavity, more satisfactorily and efficiently than merely to pour or dump the drug in the abdomen from a test tube or sterile envelope. This method also guards against the formation of lumps and small masses which may become insoluble masses and act as foreign bodies.

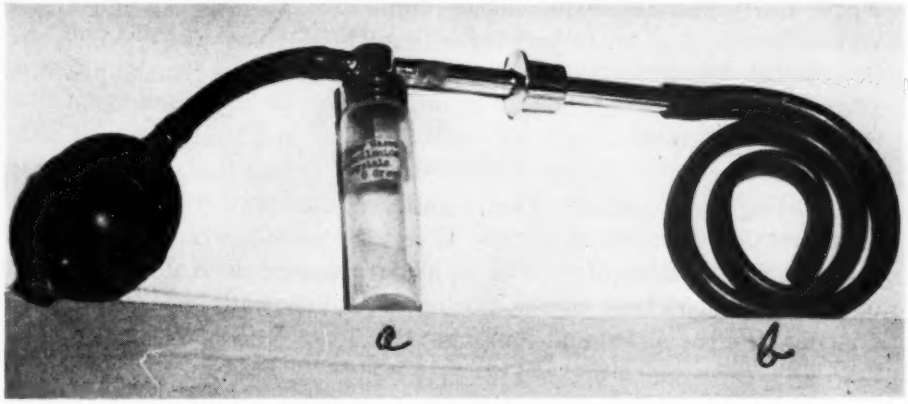

Fig. 1.—*A*, The insufflator; *B*, rubber tubing eighteen inches long.

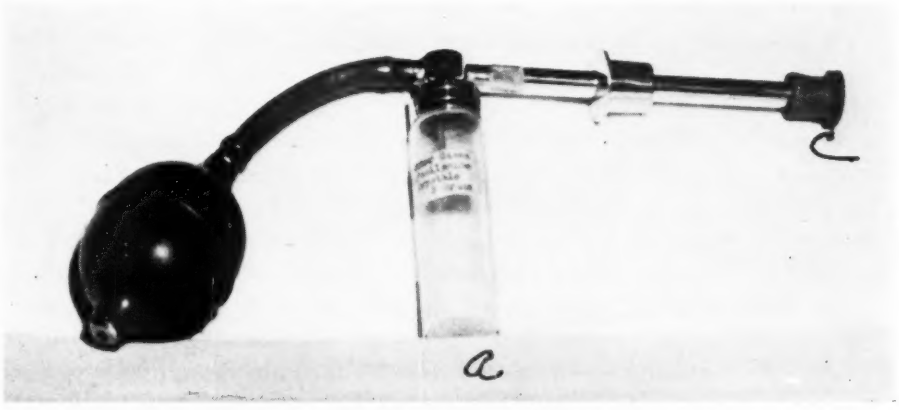

Fig. 2.—*A*, The insufflator; *C*, small piece of rubber tubing tied off at one end to protect the tip of the insufflator when not in use.

Figs. 1 and 2 show the parts of the apparatus:* The insufflator (*A*), rubber tubing eighteen inches long (*B*), and small piece of rubber tubing tied off at one end to protect the tip of the insufflator when not in use.

Received for publication, Nov. 10, 1944.

*This apparatus was made up at my suggestion but assembled by the operating room supervisor at the St. Joseph's Hospital.

It is our custom to load the sterile insufflator with 8 Gm. of sterile sulfanilamide crystals for each case in order to have an amount sufficient for implantation of the abdominal cavity to spray the drainage tract on the way out, as well as the abdominal wound itself. We use the sulfanilamide crystals, exclusively.

In the treatment of local wounds the insufflator without the attached rubber tubing is very satisfactory and permits implanting the wound thoroughly, regardless of location or position and without the danger of lump formation of the drug.

The care of the apparatus is as follows: The insufflator is wrapped in double covers and autoclaved under nineteen pounds pressure at 250° F. for thirty minutes. The rubber tubing is washed in soap and water, rinsed once in tap water and three times in distilled water, coiled up, wrapped in double covers, and autoclaved under fifteen pounds pressure at 250° F. for fifteen minutes.

COMMENTS

This simple apparatus is handy and very satisfactory, a decided improvement over any other method of which I have any knowledge. The operator has the advantage of being able to implant the drug in the form of a spray, anywhere in the abdominal cavity, without handling or traumatizing the abdominal contents.

THE VALUE OF STAPHYLOCOCCUS TOXOID IN THE TREATMENT AND PREVENTION OF CHRONIC STAPHYLOCOCCUS INFECTIONS

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INTRODUCTION

THE treatment and prevention of chronic staphylococcus infections, particularly of recurrent furunculosis and axillary abscesses, has always been one of the major problems confronting general practitioners and surgeons. It is known that the use of vaccines, various chemicals, such as "stenoxyl" and sulfanilamide derivatives, x-ray and ultraviolet irradiation, autochemotherapy, and many other methods of treatment have not fulfilled their expectations. It is natural, therefore, that the discovery of staphylococcus toxin[1-5] and its ability to produce antitoxin[6-11] attracted wide attention as a possible method of treatment and prevention of staphylococcus infections.

LITERATURE

The discovery of Burnet[12] that staphylococcus toxin could be detoxified by formaldehyde without the loss of its antigenic power, greatly simplified the matter of immunization. This led to the wide clinical use of a detoxified toxin known in different countries as toxoid or anatoxin.

Significant Factors in the Preparation of Toxoid in the Literature.—

1. *General laboratory observations:* At the present time we know of four different staphylococcus toxins, namely hemolysin, leucocidin, necrotoxin, and lethal toxin, each one causing a characteristic reaction. According to Panton and Valentine,[13] different strains of staphylococci are capable of producing these toxins in varying proportions. They have also shown that while necrotoxin, hemolysin, and lethal toxin of various strains are very similar, the strains differ considerably in the production of leucocidin. The latter view has been supported by Bryce and Burnet,[10] by Parish and Clark,[14] and by Ramon and Richou.[15]

Panton and Valentine[13] and Valentine[16] have further found that acute human infections were associated with strains which produced strong leucocidin, while sycosis, acne, and other small chronic staphylococcus infections were often caused by strains which yielded powerful hemolysin but weak or undemonstrable leucocidin. In view of these findings it becomes important that toxoid used in recurrent furunculosis should be rich in leucocidin, whereas toxoid used for sycosis and similar lesions should contain powerful hemolysin. But since, at the present, there is

Received for publication, Oct. 12, 1944.

no differentiation made in the use of toxoid for one or another type of staphylococcus infection, it is expedient that toxoids should contain all of these toxins in sufficient quantities to stimulate the production of strong antitoxin for each individual toxin. Preferably, toxoids should be made from a number of toxigenic strains isolated from representative types of staphylococcus.

2. *Culture medium:* In order to maintain a consistently high toxigenicity of any staphylococcus, the selection of an appropriate medium is essential. The semifluid medium of Burnet[12] containing 0.8 per cent agar in the 2 per cent proteose-peptone buffered broth of Parker,[5] seems to be widely used in this country and abroad. However, as different toxigenic strains vary in their nutritive requirements for the continuous production of powerful toxin, many modifications of this medium, in regard to the brand of peptone and meat base, have been proposed. It has been reported that the presence of a small amount of potassium, magnesium, and glucose are essential for the production of powerful toxin, some of these ingredients favoring the production of hemolysin and others of leucocidin. Ramon and his co-workers discovered many toxigenic strains by using synthetic media of definite chemical composition, including two indispensable ingredients, namely, nicotinic acid and thiamine chloride.

3. *Antitoxin Binding Power:* Burnet,[17] and Ramon and his co-workers[18] have found that if staphylococcus toxin and antitoxin are mixed in the proportions in which they are mutually saturated, flocculation occurs, which represents the precipitation of combined toxin and antitoxin. By means of this test it is possible to evaluate the antitoxin binding power of toxin; thereby the antigenicity of the toxin can be gauged.[8] When toxoid is prepared by the use of formalin, the flocculation reaction remains unaltered and its antigenicity may be estimated fairly accurately quantitatively.[19] These observations of Burnet, and of Ramon and his co-workers, have been confirmed by Dolman and Kitching,[20] Kitching and Farrell,[21, 22] Chaudhuri,[23] and other workers, who consider the high binding power of toxoid as determined by the flocculation test most essential in the determination of the potency of toxoid. Ramon and his co-workers believed that in order to produce a beneficial therapeutic effect, toxoid must possess an antigenic power of at least 10 units per cubic centimeter, that is, that 1 c.c. of toxoid should completely flocculate 10 international units of antitoxin.

However, in the preparation of commercial toxoids this factor apparently has not always been given due attention. The study of Farrell[24] on eleven samples of toxoids, seven of which were obtained from the open market, proved that the number of antitoxin binding (Lb)* units of these toxoids ranged from 1.2 to 51 Lb per cubic centimeter. And out of the seven samples from the open market, five contained less than ten antitoxin binding units (Lb) per cubic centimeter.

*Lb. per cubic centimeter is the number of units of antitoxin combining with 1 ml. of toxoid.

Clinical Use of Staphylococcus Toxoid.—

1. *Connaught toxoid:* The first attempt to utilize staphylococcus toxoid in the treatment of staphylococcus infections was made in 1933, in Canada, by Dolman, who was associated with the Connaught laboratories.[25] Toxoid used in this work was prepared by the addition of a 0.3 per cent solution of formaldehyde to the pooled toxins obtained from several highly toxigenic strains of staphylococci, freshly isolated from various types of human lesions. When toxin was first produced it possessed very high hemolytic, dermonecrotic, and lethal power. The leucocidin power evidently was not tested. Twenty-eight patients suffering from intractable, persistent, recurrent staphylococcus infections were treated, including sixteen cases of recurrent furunculosis. Alleviation and then apparent cure followed in all cases in the course of four to eight injections, for a total of 0.75 to 1.5 ml. given at five- to seven-day intervals. The clinical improvement could be correlated with an increased titer of circulating antihemolysin, which on the average increased tenfold.

In 1935 Dolman,[31] using Connaught toxoid, supplemented his early work with a series of 306 cases of various staphylococcus infections. In this series there were eighty-one cases of recurrent furunculosis, the others being acne, staphylococcal infections of the nose, throat, and nasal sinuses, recurrent abscesses, and fifty-nine cases of chronic osteomyelitis. He observed that the clinical evidence of the acquisition of immunity was usually apparent after two to three injections. By this time the boils showed rapid regression and new ones stopped appearing. In some cases of recurrent furunculosis, as many as twenty injections had to be given in order to prevent recurrences. In all recurrences the patients carried toxigenic strains of staphylococcus in the anterior nares. The latter finding was confirmed by Valentine.[16]

Gilchrist and Wilson[32] successfully used Connaught toxoid in the treatment of sixty-five cases of staphylococcal infections of the upper respiratory tract in patients with diabetes, with only three failures.

2. *Burroughs Wellcome toxoid in England:* Using four injections for a total of 0.75 ml. of Burroughs Wellcome toxoid prepared in England, Connor and McKie,[26] Connor,[27] and Gohar[28] reported similar clinical and serologic findings in a group of patients suffering from furunculosis and sycosis. Their toxoid was prepared from the pooled toxins of four strains of staphylococci and detoxified with 0.2 per cent formaldehyde.

Similarly favorable results with Wellcome toxoid were obtained by Parish, O'Meara, and Clark[29] in the treatment of recurrent furunculosis. The rapid increase of the antihemolysin titer and the correlation with clinical improvement made them feel that circulating antitoxin is of value in combating the infection.

Using six injections for a total of about 2 ml. of Wellcome toxoid, Murray[30] reported encouraging results in a group of 116 cases of various superficial chronic staphylococcal infections. The antihemolysin titer,

which in untreated cases was usually on an average of 1 unit, reached an average of 7.6 units one week after the fourth injection. This amounted to an increase of eight times that of the initial titer. Eighty-one patients who had recovered were seen after a period of two to five months or more; in thirteen, relapses had occurred, but the lesions were usually not severe. Results in acne were less encouraging than in other infections.

Using Wellcome toxoid, Whitby[33, 34] obtained encouraging results in a group of 200 cases. Of these, 117 were cases of furunculosis, some cases of styes, some of pustular acne, sycoses, and other superficial staphylococcal infections. Seventy-six out of 117 patients with furunculosis recovered rapidly, however, 25 per cent of these had relapses. A second course brought relief, but only continued monthly doses succeeded in preventing further relapses. There was no success in the treatment of acne and sycosis. The variability of individual serum responses to a set dose of toxoid, and the lack of correlation between the antihemolysin titer and the clinical picture, caused Whitby to conclude that the response to antigen is a highly individual reaction.

The clinical results of Smith,[35] who used Wellcome toxoid in twenty cases of recurrent furunculosis, were less encouraging than the results of previous workers. Similarly to the results of Whitby, there was no correlation between antihemolysin titer and clinical results.

3. *Pasteur Institute toxoid:* A considerable amount of laboratory and clinical work with staphylococcus toxoid was done by the French workers Ramon, Bocage, Richau, and Mercier of the Pasteur Institute in the hospitals of Paris.[36-41] They believed that the clinical success of toxoid treatment was directly related to the degree of antigenicity of the staphylococcus toxin, from which the toxoid is derived. The antigenicity of the toxin was tested by the flocculation method applied by Ramon[42] in testing diphtheria toxin. Several strains of staphylococci, including one freshly isolated from the blood of a patient with septicemia and another from a case of furunculosis, were used in the preparation of their toxoid. For detoxification, 0.3 to 0.5 per cent formaldehyde was used. This toxoid has been used by Ramon, Bocage, Richau, and Mercier in over 2,000 cases of various staphylococcal infections. The usual course consisted of 0.1, 0.25, 0.5, 1.0, and 2.0 ml. injections given at five-day intervals. Of 1,000 cases, mostly multiple and recurrent furuncles and carbuncles, there was rapid recovery in at least 90 per cent. When the furuncles were treated at the onset, they did not suppurate, and dried out within three to five days. Extension of furuncles in cases of multiple furunculosis usually stopped after two, and not more than three, injections. Having followed many of the cases for about four years these workers observed recurrences in only about 10 to 15 per cent of the cases. This toxoid and other similarly prepared toxoids were used widely by numerous French and other European workers.

Tzanck, Klotz, and Negreanu[43] treated fifty-six patients with various staphylococcal infections, with only three failures.

Excellent results were reported by Simon,[44] Debre, Bonnet, and Thieffry,[45] Decoulx and Patoir,[46] Laurent and Tardy,[47] Gaté, Guilleret, and Chanial,[48] Ungerer,[49] Moulier,[50] Soupault and Levy-Bruhl and Moulier,[51] and many other workers, listed in the work of Ramon and co-workers.[38]

Using the same preparation and technique, Riou and Bigot[52] treated at Tonkin, 126 patients with staphylococcal infections with satisfactory results; those suffering from furunculosis usually had numerous lesions. One of these patients had had 376 boils and another 283. Both patients were greatly relieved after two injections and apparently cured after three.

Nélis,[53] and Nélis and van Mechelen of Belgium[54] treated sixty-five cases of furunculosis among miners, with ten injections of the same toxoid; fifty-seven of the sixty-five patients recovered rapidly.

Nélis and Piérard[55] treated a total of 300 patients and reported excellent results.

In Italy, Caminiti[56] and Perogallo[57] treated furuncles, general abscesses, and axillary abscesses with satisfactory results.

Similar reports came from Simitch and Djourichitch[58] in Belgrad, Bruck in Sweden,[59] and Montant and Dernaz in Geneva,[60] who observed that anatoxin produced the best results in axillary abscesses and acute and chronic furunculosis.

Many of these workers used the antihemolysin test as the measure of immunity and observed a rapid increase of antihemolysin titer following the toxoid injections.

Four to twenty times' increase in antihemolysin titer was observed by Mercier after a single injection of 0.5 c.c. of toxoid, and four- to thirty-five-fold increase was produced by a series of injections.

On the other hand, the antihemolysin titer of patients treated by Ramon and his co-workers[36] in his early work, and by Nélis and his co-workers, usually did not exceed 5 units, 2 to 3 units being the average. The original titer of their patients usually ranged between 0.25 to 1 unit.

Thus, numerous and almost consistently enthusiastic reports have come from Europe, Canada, and the French Colonies concerning the use of formaldehyde toxoid. In all cases it was prepared from the pooled toxins of several highly toxigenic strains of staphylococci obtained from various sources. Toxoid prepared at the Connaught laboratories and the Pasteur Institute was characterized by a high antigenicity, the index of which was its binding power with antitoxin as determined by the flocculation test. No information on the antitoxin binding power of Wellcome toxoid was obtained.

Contrary to these numerous and highly encouraging results on toxoid therapy in various staphylococcus infections from abroad, the reports on the use of toxoid in the United States are comparatively few, and in

the majority of instances discouraging. Furthermore, the toxoid therapy of recurrent furunculosis, which constitutes the main group of the cases treated abroad, is scarcely reported in this country. This fact seems to be significant, for it is seldom that negative results are reported.

4. *Lederle formalized and pepsin digest toxoid, and toxoid prepared by other commercial firms in the United States:* American reports deal mostly with chronic low-grade staphylococcus infections, such as acne vulgaris, conjunctivitis, and sycosis barbae. One report deals with the toxoid treatment of chronic osteomyelitis.

Kindel and Costello[61] and Cornbleet and Rattner[62] reported negative results in a group of forty-two and twenty-three cases, respectively, of cases of acne vulgaris and sycosis barbae and furunculosis. The toxoid used by these workers was an unnamed commercial preparation made of a single (Burky) strain of staphylococcus which was converted into toxoid by adding 0.2 per cent formaldehyde. A total of at least 2.0 c.c. was given in repeated doses at weekly intervals.

More encouraging results in acne were obtained by Tanenbaum, Joyner, Speed, and Bremer,[63] who used the formalized toxoid of Lederle* on 100 cases of acne among students. Using a large number of injections of toxoid which began with 0.1 c.c. of dilutions 1:100 or 1:1000 and terminating with 1.0 c.c. of undiluted toxoid, these authors obtained encouraging results in 58 per cent of the cases.

On the other hand, Sulzberger and Rubin (in a discussion[63]), having used the same toxoid in similar cases in older individuals, received benefit in only six out of twenty-five cases.

Thygeson[64, 65] obtained some encouraging results in the treatment with Lederle's toxoid in 140 cases of blepharoconjunctivitis. Using formalized toxoid in a group of fifty-seven cases he obtained healing in twenty-one and clinical improvement in nineteen others. Later, treating eighty-three patients with Lederle's pepsin digest toxoid,† he obtained a larger percentage of clinical improvements but a smaller percentage of complete recovery.

On the other hand Julianelle, Boots, and Harrison,[66] having used Lederle's toxoid (apparently pepsin digest), in thirty cases of chronic conjunctivitis failed to notice any beneficial effect in their patients. Antihemolysin tests carried out by Thygeson and by the latter workers, showed an average increase of 3 units, but there was no correlation with the clinical results.

Buchman[67] reported on the use of Lederle formalized toxoid in a group of thirty-eight cases of chronic osteomyelitis with negative results. He observed an increase of the antihemolysin titer of two to thirty-four times in the majority of his patients. However, this increase

*Personal communication with Joyner revealed that the toxoid was prepared from the toxin of two staphylococcus strains called "Wood" and "Blair."

†Pepsin digest toxoid was prepared from "Wood" and "Blair" strains and was detoxified by digestion with pepsin. It possessed no antitoxin binding power.

did not expedite the healing of the existing lesions, nor did it prevent the development of new ones.

Longacre[68] used pepsin digest toxoid of Lederle on thirty-five cases of various staphylococcus infections in the Vanderbilt Clinic, Columbia-Presbyterian Hospital. The majority were cases of acute and recurrent furunculosis. Some of these patients showed an immediate clinical improvement; however, when followed by us, most of them developed recurrences. There was an average increase of antihemolysin titer in the majority of these patients up to 2 to 4 units, however, no correlation was found with the clinical results.

Thus in this country, where the treatment of staphylococcus infections has met with small success, we found that the toxoid generally used has been derived by formalization or pepsin digestion of toxins of a single, or at most two, strains of staphylococci. The lesions from which these staphylococcal strains had been isolated were not similar to those in which toxoid was being applied therapeutically, and the binding power of toxoid with antitoxin as estimated by the flocculation test was either not tested as in formalin toxoid or was definitely absent as in pepsin digest toxoid.

OUR LABORATORY AND CLINICAL RESULTS WITH LEDERLE TOXOID

In collaboration with Dr. E. Howes, in 1936, we initiated the use of Lederle's formalized toxoid in the Vanderbilt Clinic. However, after having treated a group of twenty patients suffering from recurrent furunculosis, we failed to notice any marked clinical improvement in the course of treatment. We found further that the prevention of recurrences by this method in about 50 per cent of the cases was no higher than that obtained with staphylococcus stock or autogenous vaccine. It was also noted that the injections were often followed by a severe local reaction and frequently by a systemic reaction.

Our interest in toxoid was revived when the modification by the peptic digestion method of Parfentjev was introduced. The neutralization of a large proportion of protein by digestion with pepsin considerably decreased the nonspecific protein reaction and allowed for injections with larger doses of more concentrated toxoid. This study comprised a group of 200 cases of staphylococcus infections. The majority of these were cases of recurrent furunculosis, most of which had formerly proved resistant to other forms of therapy. The rest consisted of axillary abscesses, cases of acute multiple furuncles and carbuncles. A majority of the patients were treated with Lederle peptic digest toxoid alone. Some patients received a combined treatment with Lederle toxoid and autogenous vaccine* and a few were treated with vaccine alone. The

*A twenty-four-hour culture grown on a 5 per cent human blood slant, isolated from the patient's lesion, was washed with 10 c.c. of physiologic saline solution. This washing was diluted down to approximately 200 million bacteria per cubic centimeter and 0.3 per cent formaldehyde added. It was stored in the refrigerator until no growth appeared on plating.

course of toxoid injections was as follows: On the day following the skin sensitivity test, which consisted of a subcutaneous injection of 0.1 c.c. of toxoid in 1:100 dilution, 0.1 c.c. of a 1:10 dilution of toxoid was given subcutaneously. This was followed at three- to five-day intervals with 0.1, 0.25, and 0.5 c.c., and five doses of 1.0 c.c. of undiluted toxoid. In another group of cases the skin sensitivity test was done with 0.1 c.c. of undiluted toxoid and this was followed with 0.25 and 0.5 c.c. and five 1.0 c.c. doses, the total quantity being 5.85 c.c. In those cases where recurrences developed continuously despite injections, the treatment was continued for a longer period of time, depending upon the individual case. Those cases in which recurrences came following the completion of a series of injections were given a second, a third, and in some cases even a fourth series of injections.

The sera of all patients were tested for antihemolysin titer prior to the initiation of the course of injections. This testing of sera was repeated after the fourth and seventh injections and in some patients from two weeks to one month following the completion of the series. Whenever recurrences developed the serum was tested before initiating a new course. The sera of many patients were sent to the Lederle Laboratories where they were tested for antileucocidin titer, and wherever the quantity was sufficient, mouse protection tests were performed.

Out of the entire group, we are presenting only the results of those cases in which the patient received a complete course of toxoid injections and those which we were able to follow up for a period of three months to two years. The results are shown in Tables I to IV.

TABLE I

RESULTS WITH LEDERLE TOXOID SHOWING THE PERCENTAGE OF RECURRENCES IN THE TWO MAIN CATEGORIES OF TREATMENT

	TOTALS	RECURRENCES	PER CENT RECURRENCES	
Recurrent furunculosis	93			
Lederle toxoid	80	49	61.3	61.2
Lederle toxoid and vaccine	10	6	60.0	
Vaccine alone	3	2	66.7	
Axillary abscesses	18			
Lederle toxoid	13	9	69.2	61.2
Lederle toxoid and vaccine	5	2	40.0	

TABLE II

RESULTS WITH LEDERLE TOXOID SHOWING THE LACK OF CORRELATION BETWEEN THE RISE OF ANTIHEMOLYSIN AND ANTILEUCOCIDIN AND THE CLINICAL RESULT

CASE NUMBER	ANTIHEMOLYSIN		ANTILEUCOCIDIN		RECURRENCES
	BEFORE	AFTER	BEFORE	AFTER	
1	3u	10u	0.32	0.64	+
2	1u	6u	0.32	0.24	0
3	1.5u	8u	0.12	0.03	+
4	2u	4u	0.64	0.64	+
5	<1u	1u	0.15	0.2	0
6	6u	8u	0.04	0.32	±

CLINICAL RESULTS

Some cases showed immediate clinical improvement; however, these occurred in an earlier series and were very rare among the patients of the later group.

There were also many recurrences during the course of injections of Lederle toxoid. Thus, out of eighty patients with recurrent furunculosis, forty-nine developed recurrences. Of these, forty-one had recurrences following at least three injections; in twenty there were multiple recurrences. The percentage of recurrences of axillary abscesses treated with Lederle toxoid was very similar. Those treated with toxoid and vaccine gave about the same percentage of recurrences. There were no recurrences following the treatment with Lederle toxoid among five patients with acute multiple furunculosis and two with carbuncles.

SERUM ANTIHEMOLYSIN TITERS IN RECURRENT FURUNCULOSIS TREATED WITH LEDERLE TOXOID

The antihemolysin titer before the initiation of treatment in the majority of recurrent furunculosis ranged from <1 to 1.5 units. After a series of seven or more injections, there occurred in one-half of the cases, a rise in titer to between 1 to 2.5 units, while in the other one-half it reached 3 and rarely 4 to 10 units. Thus, in only one-half of the cases did the titer reach 3 units, the level which, according to Ramon and his co-workers, affords a certain degree of protection.

A smaller number of antileucocidin and mouse protection tests were carried out,* but there was no apparent consistency in the correlation of these tests either with the rise in antihemolysin titer or in clinical results.

SKIN SENSITIVITY AND POLYSACCHARIDE TESTS

When the skin sensitivity test was run with a dilution of 1:100 of toxoid, a reaction was lacking or negligible before, during, or following the injections.

When, however, the skin sensitivity test was run with undiluted toxoid, the reaction during and following the end of treatment usually was more marked than before the treatment started. This seems to indicate a growing sensitivity to intracutaneous injections of toxoid during treatment.

Along with skin sensitivity tests, before and after injections, Julianelle's polysaccharide test was tried on the patients. However, the results were almost always negative and showed no correlation with an increase in the antihemolysin titer or with recovery.

CLINICAL AND LABORATORY RESULTS WITH CONNAUGHT TOXOID

The results obtained in recurrent staphylococcus infections with Lederle toxoid, both formalized and pepsin digested, being unsatisfac-

*In the Lederle Laboratory under the supervision of Miss Frances Clapp.

TABLE III

RESULTS WITH CONNAUGHT TOXOID SHOWING THE NUMBER AND PERCENTAGE OF RECURRENCES CORRELATED WITH THE ANTIHEMOLYSIN TITER IN RECURRENT FURUNCULOSIS

CASE NUMBER	ANTIHEMOLYSIN TITER		RECURRENCES		NOTES
	BEFORE TOXOID	AFTER 7 OR MORE INJECTIONS	DURING COURSE OF TREATMENT	WITHIN 1 YEAR AFTER TREATMENT	
1	1u	8u	0	0	Recur. after Lederle toxoid
2	2u	–	0	0	Recur. after Lederle toxoid
3	1u	8u	0	0	
4	<1u	6u	+	+	
5	1u	–	+	0	
6	1u	–	+	0	
7	1u	1u	0	0	
8	2u	4u	+	0	
9	1u	4u	+	0	
10	1.5u	8u	0	+	
11	1.5u	4u	0	0	
12	<1u	–	0	0	
13	2u	–	+	0	Diabetes
14	<1u	6u	+	0	
15	2u	3u	0	0	
16	8u	above 8u	+	+	Diabetes
17	<1u	4u	0	0	
18	1u	6u	0	0	
19	1u	–	+	0	
20	4u	8u	0	+	Recur. after Lederle toxoid
21	1u	6u	0	0	Recur. after Lederle toxoid
22	1.5u	2u	0	0	
23	1u	–	0	0	Recur. after Lederle toxoid
24	2u	–	0	0	Recur. after Lederle toxoid
25	1u	10u	+	+	Recur. after Lederle toxoid
26	1u	–	+	+	Single mild rec. in 1 month, none afterward
27	<1u	12u	0	0	
28	1u	5u	0	0	
29	1u	6u	0	0	
30	<1u	4u	0	0	
Total	30	21	11 (31.7%)	6 (20%)	

tory and inconsistent with the beneficial results reported by other workers, we felt that a similar study should be made with a toxoid yielding more favorable results in other hands.

Dr. Farrell very generously supplied toxoid made in the Connaught Laboratories in Toronto. This had been successfully used by Dolman[25, 31] and by Gilchrist and Wilson.[32] With this material, data have been obtained on an additional group of sixty-five patients.

The toxoid was given subcutaneously at five- to seven-day intervals. First dose of 0.05 c.c. was followed by 0.1, 0.15, 0.2, 0.25, 0.3, 0.4, and finally 0.5 c.c. for a total of 1.95 c.c. In the case of recurrences another series was given. Out of sixty-five patients treated, we are presenting only a group of forty patients, who received at least seven injections of toxoid and could be followed for at least one year. Of this group there were thirty cases of recurrent furunculosis and ten of recurrent axillary abscesses, alone or in combination with general furunculosis. From the accompanying Tables III and IV it is seen that recurrences during the course of the toxoid injections occurred in sixteen cases. However,

TABLE IV

RESULTS WITH CONNAUGHT TOXOID SHOWING THE NUMBER AND PERCENTAGE OF RECURRENCES CORRELATED WITH THE ANTIHEMOLYSIN TITER IN AXILLARY ABSCESSES

CASE NUMBER	ANTIHEMOLYSIN TITER		RECURRENCES		NOTES
	BEFORE TOXOID	AFTER 7 OR MORE INJECTIONS	DURING COURSE OF TREATMENT	WITHIN 1 YEAR AFTER TREATMENT	
1	1u	2u	0	+	
2	2u	4u	+	0	
3	2.5u	4u	+	+	Recur. after Lederle toxoid
4	<1u	–	+	0	
5	<1u	4u	0	0	
6	1.5u	1u	+	+	
7	1u	6u	0	0	Recur. after Lederle toxoid
8	1u	–	0	0	
9	3.5u	5u	0	0	Recur. after Lederle toxoid
10	<1u	1.5u	+	0	
Totals	10	8	5 (50%)	3 (30%)	

after the end of the treatment there were only nine recurrences, which occurred within one year of the follow-up. Ten of the patients had been previously treated unsuccessfully with Lederle toxoid. Of these, seven recovered following the injections of Connaught toxoid. The differences between the percentages of recurrences for the Lederle and Connaught toxoids are statistically significant in favor of the Connaught toxoid.

Out of twenty-nine cases in which the antihemolysin titer was tested prior to and following a series of seven or more injections, twenty-three had 4 units or higher. In general, the serum of the patients who recovered was characterized by a high antihemolysin titer. However, there were exceptions in which recurrences developed in spite of the high titer of the antihemolysin; while in some other cases the recovery was complete in spite of the fact that the antihemolysin titer was below 3 units.

The data on the antileucocidin titer of the sera of the treated patients indicate that, although there seems to have been a slight increase following the treatment, there was no correlation with antihemolysin titer or with the clinical results. However, having complete data on only nine patients, we feel that more work should be done in order to make a definite assertion on this point.

DISCUSSION

The problem of recurrent staphylococcus infections in the form of furuncles and carbuncles frequently plagues the general practitioner and the surgeon. It is well known that certain individuals are generally resistant and others generally susceptible to infections. Others who have been resistant suddenly become susceptible. No reliable test has been discovered to measure either the resistance or the susceptibility to staphylococcus infections, although many attempts have been made

to find such a test. Normal individuals do not have a high antihemolysin titer and there must be some other element of immunity which is responsible for natural resistance. Many immunologists believe that it resides in the phagocytic power of the leucocytes, but this cannot be consistently demonstrated.

When a staphylococcus infection becomes established in the skin, local recurrences in the neighborhood suggests that the organisms get out of the original lesion and get into neighboring pores. Recurrences can be minimized by precautions taken by the patient (1) to avoid contact with the lesion by his hands, (2) to wash the hands frequently, and (3) to avoid rubbing or scratching in other areas.

The lesions themselves can frequently be aborted or their course shortened by the local injection of either penicillin or potent staphylococcus bacteriophage, and the inhibition of bacterial activity by these agents renders the organisms discharged from the lesions onto the surrounding skin less likely to gain a foothold if rubbed or scratched into other areas of the skin. This has been demonstrated in many of the cases included in this series. Neither penicillin nor bacteriophage, however, has any influence on the resistance of the individual to subsequent recurrences if there is a free interval of time after the complete subsidence of the initial infection. Therefore, the problem of building up a resistance to subsequent infections is of very great importance and must be met in some other way.

Careful analysis of the laboratory and the clinical data on staphylococcus toxoid collected by numerous workers, together with our own observations, have revealed certain factors which we feel may help practitioners and surgeons in the solution of this problem.

Favorable reports came out of Canada where Connaught Laboratory toxoid was used, and out of many European countries where toxoid prepared at the Pasteur Institute of Paris has been used. These toxoids were formaldehyde-detoxified pooled toxins of a number of toxigenic staphylococcus strains, obtained from a variety of lesions. Consequently, toxoids used in both Canada and Europe possessed multiple antigenicity. In the preparation of these toxoids the workers realized the importance of using strains isolated from lesions similar to those being treated. These strains produced strong leucocidin, which is characteristically associated with acute and severe infections. The criterion of potency of both products was a high binding power with antitoxin, which was found by many workers to be closely related to the antigenicity. This was determined by the flocculation method.

The clinical results obtained with Wellcome toxoid in England, although encouraging, seem to be on the whole less favorable than those obtained with Pasteur and Connaught toxoid. The description of their method of preparation did not disclose whether it included any strains from furunculosis or similar lesions, which produced high leucocidin. Neither was the toxoid tested for its binding power with antitoxin. The importance of the criteria of potency as applied by the French and

Canadian workers in toxoid preparation such as multiple antigenicity, high binding power with antitoxin, and consequently a rapid antibody production in vivo, becomes apparent when we analize the toxoid which was used with discouraging results. Kindel and Costello, Cornbleet and Rattner, Buchman, Longacre, and we ourselves in the first group of cases used toxoid in which at least two of these criteria were not fulfilled. Toxoid was prepared from one, or at most from two, strains. Pepsin digest toxoid of Lederle possessed no binding power for antitoxin. The antigenicity was apparently not high, since of a group of six patients treated by Dr. A. Coca at the Lederle Laboratories, only one "who had an average of seven injections of toxoid, reached an antihemolysin titer of 4 units, the remaining five reaching a maximum of 2 units."[69] Similar titers were obtained following seven injections in our group of patients treated with Lederle pepsin digest toxoid. A desire to eliminate nonspecific protein reactions, local as well as systemic, led to the introduction of the pepsin digest process for the conversion of toxin into toxoid. Apparently, however, the pepsin digestion resulted in a decrease of the antigenicity of toxoid for human beings although the antihemolysin titer in rabbits did not significantly differ from the one produced by the formalized product. Besides, the persistence of a still significant local reaction seems to indicate that although practically all the protein was neutralized by digestion with pepsin, an incomplete detoxification occurred. This is shown by the appearance of hemolysis of rabbit blood cells after overnight standing and an extremely severe reaction when toxoid containing Lyons' strain, which produced strong leucocidin, was included in the preparation of toxoid.

As to the mechanism of the action of toxoid therapy: Is its role only to stimulate the production of antitoxin against hemolysin, leucocidin, and dermonecrotizing toxin?

Undoubtedly the production of antitoxin is an essential factor in inducing immunity. This has been shown by many animal experiments in which protection against living staphylococci was attained by toxoid injections but not by vaccine injections.

Toxoid also contains nonspecific proteins which may induce a reaction similar to the nonspecific protein shock therapy.

There are also nonspecific defense factors of the body, particularly phagocytoses, which were reported to have been stimulated by the increase of antitoxin to the blood. It should also not be forgotten that toxoid contains bacterial antigens stimulating the production of bacteriotropins, agglutinins, and bacteriolysins.

However, if these bacterial antibodies are to be of value in combating the causative organisms, they must be stimulated by a strain closely related to that producing the lesion. In testing bacteriophage susceptibility of staphylococci isolated from various lesions, we have found that strains possessing the same morphologic and biologic characteristics differed in their phage susceptibility according to their source and the duration of infection.

Thus staphylococci, isolated from acute osteomyelitis, were more susceptible to phage than those of chronic osteomyelitis. The staphylococci causing conjunctivitis or sinusitis displayed only partial susceptibility to phage, while staphylococci isolated from acute infections such as furunculosis or septicemia were completely susceptible in 95 per cent of the cases. However, if phage was adapted to one strain from a case of sinusitis it was often found to become completely effective against the majority of strains from similar lesions. The same was found to be true with cases of conjunctivitis. It is our belief, following these observations, that in order to be effective against one or another type of infection, toxoid should necessarily include toxigenic strains of bacteria isolated from lesions similar to those being treated. It is possible that the success of Thygeson in the toxoid therapy of chronic blepharoconjunctivitis might be partially attributed to a closer antigenic relationship between the strain used in toxoid preparation and the strains causing this infection. It might also be attributed to the production by the Wood strain of a powerful hemolysin, which is likely to be characteristic of staphylococci causing this infection.[13, 16]

The antibacterial body antigen which is comparatively scarce in toxoid might be better supplied in the form of vaccines. Analysis of clinical results obtained with staphylococcus pepsin digest toxoid in the Vanderbilt Clinic have shown that the therapeutic effect of this preparation was unsatisfactory. Considering that a certain percentage of patients with recurrent furunculosis recover spontaneously, the recurrences in forty-nine out of eighty cases of recurrent furunculosis and in nine out of thirteen cases of axillary abscesses seem to be indicative of the lack of the therapeutic value of that toxoid. This conclusion seems to have been further supported by the uninterrupted recurrences during treatment in many of the cases. An increase of the skin reaction following the course of injections of toxoid seemed even to indicate an increased sensitivity to toxoid, which was possibly caused by the modification of protein by pepsin digestion.

Furthermore, we feel that in spite of a frequent correlation of high antihemolysin with clinical success, it is not the antihemolysin titer which determines the state of immunity, but rather that an increase in antihemolysin parallels a raise of antileucocidin, which is the more important factor in immunity against staphylococci causing recurrent furunculosis. Unfortunately, however, the present technique of the antileucocidin test as described by Valentine does not allow clear-cut results. A certain amount of destruction of the leucocytes, due to manipulations in obtaining a concentrated leucocyte suspension, makes the microscopic interpretation of the results extremely difficult and uncertain. A simple test, perhaps on the line of the Parker Weld[70] leucocyte agglutination test, might be used for the measurement of the antileucocidin power.

It has been the experience of many workers that clinical success in staphylococcus infections is most frequently associated with a sharp and immediate rise of antihemolysin titer, rather than a slow prolonged course in reaching the same level. We feel that in those cases where a very slow rise of blood titer necessitated a prolonged treatment, along with an increased immunity to exotoxins, there may have developed a hypersensitivity to bacterial proteins.

SUMMARY

1. The treatment of ninety-three patients with recurrent furunculosis and axillary abscesses with Lederle's pepsin digest toxoid resulted in a complete recovery of only 38 per cent. In the other 62 per cent, recurrences developed within one year after the end of the treatment.

2. Of the seventy patients who received at least seven injections of Lederle's pepsin digest toxoid, the antihemolysin titer in fifty-two cases (74 per cent) ranged between 1 and 3 units and in eighteen (26 per cent) it was between 3 and 10 units.

3. Out of forty patients with recurrent furunculosis and axillary abscesses treated with Connaught toxoid, complete recovery occurred in thirty-one (78 per cent). Nine others (22 per cent) developed recurrences within one year after the end of the treatment. In five of the cases the recurrences were milder than prior to the treatment.

4. Of twenty-nine patients tested following seven or more injections of Connaught toxoid, the antihemolysin titer of the sera in twenty-three (79 per cent) ranged between 4 and 12 units; only in six (21 per cent) was it 3 units or less. These are statistically significant differences.

5. The antihemolysin test is not a strict measure of immunity, for there are exceptional cases in which the patient has a rise in titer and has recurrences, and others who have no rise and yet seem to be cured.

7. There may be some other immune factor which does not run strictly parallel with the antihemolysin titer which is of major importance but cannot be measured.

CONCLUSIONS

Staphylococcus toxoid, made from toxigenic strains, is able, by means of repeated injections, to increase the antihemolysin titer of the blood and to lessen significantly the incidence of recurence of furuncles and carbuncles.

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PLASTIC SURGERY IN RECONSTRUCTING ENLARGED BREASTS

One-Stage Mastopexy

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THE plastic surgeon is often called upon to reconstruct enlarged and deformed breasts. With such deformity, aside from mental embarrassment, the patient suffers from physical disability. The posture is poor, the shoulders are rounded, shoulder strap marks are painful, and the excess weight of the breasts enervates the individual.

Numerous papers have reviewed the literature and discussed the evolution of the surgical methods.[2, 3, 6, 7] It is our purpose to evaluate the end results of several procedures so that their applicability to the specific case may be judged. Two factors must be thoroughly understood in order to appraise the method of approach: (1) the anatomy and physiology of the breast and (2) the type of deformity and pathology involved.

SURGICAL ANATOMY AND PHYSIOLOGY

Embryology.—Early in the development of many mammals a slight ectodermal ridge appears along the side running from the axilla to the groin. As the embryo develops these ridges disappear into a series of pyramids, each forming a slight elevation and constituted of ectodermal cells. These are the anlagen of the future mammary glands. In the human being, they are always in excess to the number of mammary glands normal to the species. However, should an extra one persist, a supernumerary breast occurs, while if there is a suppression of all these anlagen, there is an absence of the mammary gland. Should a suppression occur on one side, then only one normal breast will develop.

The mammary gland may be regarded as analogous to the sweat gland. Commencing as a stalklike growth in the derma, it envelops its way into the superficial fascia. It then develops several branches which extend in various directions, push deeper, and finally rest on the covering of the pectoralis major muscle. Most of the fat, therefore, comes to lie between the glandular structure and the skin. Thus, in early youth the breast is shaped by the adipose tissue.

Blood Supply.—Superiorly, the mammary gland receives its circulation from the axillary artery which gives off the pectoral branch of the acromial thoracic artery at the inner border of the pectoralis minor muscle. It descends between the pectoralis major and minor, anastomosing with the intercostals and the long thoracic artery. Medially, the breast is supplied by the perforating branches of the internal

Presented in abridged form in conjunction with colored surgical motion pictures at the Los Angeles County Medical Association, May 11, 1944.
Received for publication, July 3, 1944.

mammary artery from the second to the sixth interspace. Laterally and inferiorly, the long thoracic artery descends along the lateral edge of the pectoralis major muscle to the mammary gland. The short thoracic and superior thoracic vessels also send branches to the breast. Contributing further to the blood supply of the gland are the upper five or six anterior intercostal arteries.

Lymphatics.—The breast possesses an excellent lymphatic supply. The superficial chain anastomoses with the deep chain to form a plexus around the nipple. The deep chain is situated around the lobules and ducts. Both sets drain to the lymph nodes in the axilla and those surrounding the pectoralis major muscle and communicate with the subclavicular region and the anterior mediastinum.

Nerves.—The breast tissue and the surrounding skin are supplied by the brachial plexus through its thoracic branches, by the descending branches of the cervical plexus, by the anterior cutaneous plexus of the third, fourth, and fifth intercostal nerves, and the anterior divisions of the lateral cutaneous branches of these nerves. The second and third intercostal nerves anastomose to supply sensation to parts of the breast, as well as to some of the surrounding skin of the adjacent thoracic area. The parenchyma receives little sensory nerve supply, so that minor secondary surgical repair, when required, may be carried out adequately under local anesthesia.

The nipple is highly supplied with sensory nerves. However, its erectibility occurs irrespective of its nerve supply. Thus, when a nipple transplant is performed, the nipple is able to gain erection before it has attracted any nerve supply to its new residence. This inherent ability is due to the contractions of the circular muscle fibers of the base.

Physiology.—The secreting structure of the breast consists of some twelve to sixteen lobules and their individual ducts. Beginning in the acini, the lactiferous ducts terminate in the nipple. Below the nipple each duct forms a sinus.

The glandular tissue of the breast is irregular and possesses three projections, one going medially ending adjacent to the sternum while the other two extend at an angle toward the axilla, one above and one below. In anomalous cases, the glandular tissue may extend much further and in variable directions.

The nipple possesses both longitudinal and circular smooth muscle. The former is attached to the lactiferous ducts and retracts the nipple, while the circular fibers erect the nipple. The areola surrounds the nipple and following pregnancy or hypertrophy it becomes more pigmented. The tubercles of Montgomery found within the areola are sebaceous glands which secrete milky fluid.

The fibrous septa of the superficial fascia continue into the breast to surround the fatty and glandular tissue. These fibrous structures are attached to the skin and envelop themselves between the cells and the

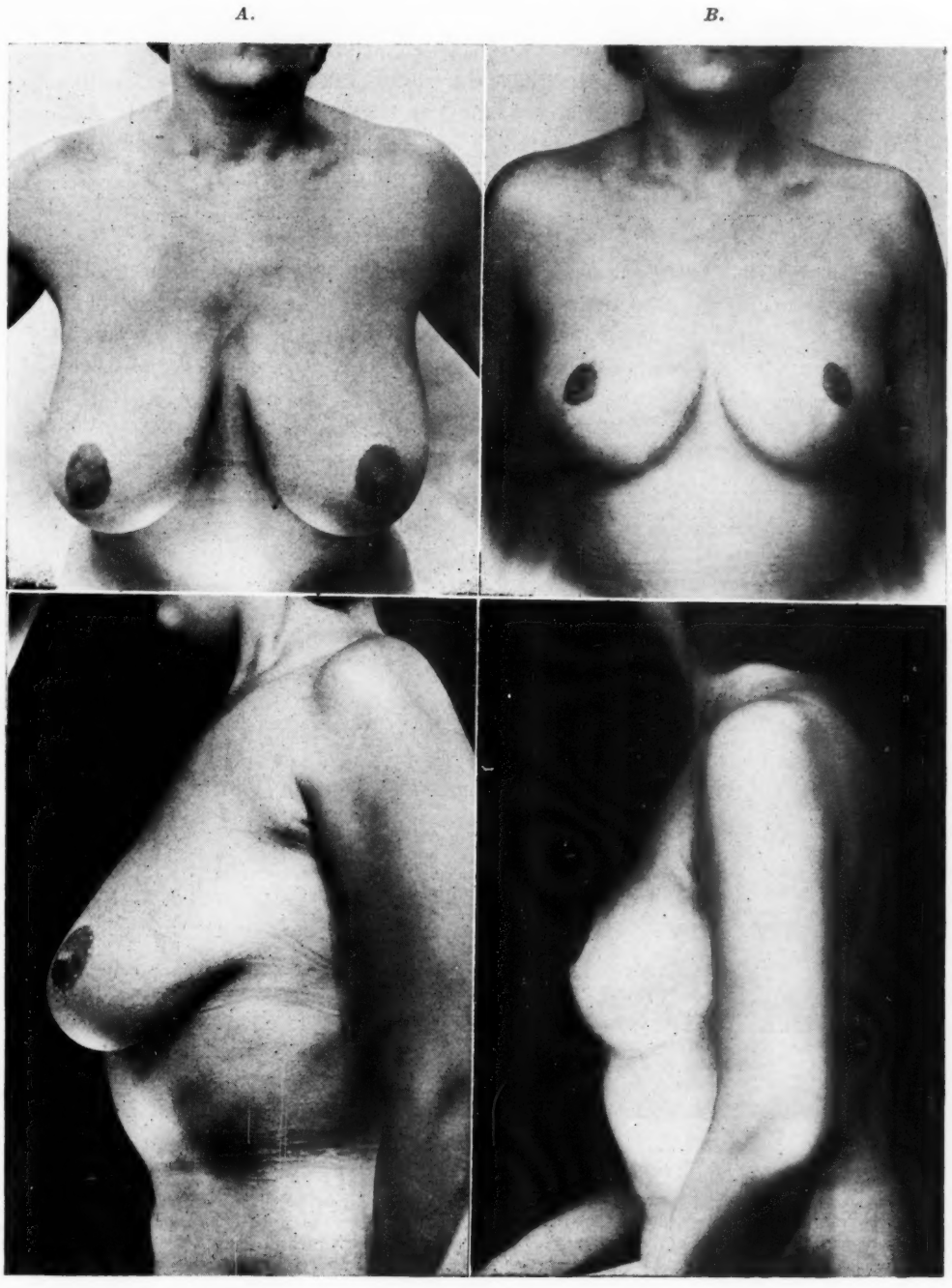
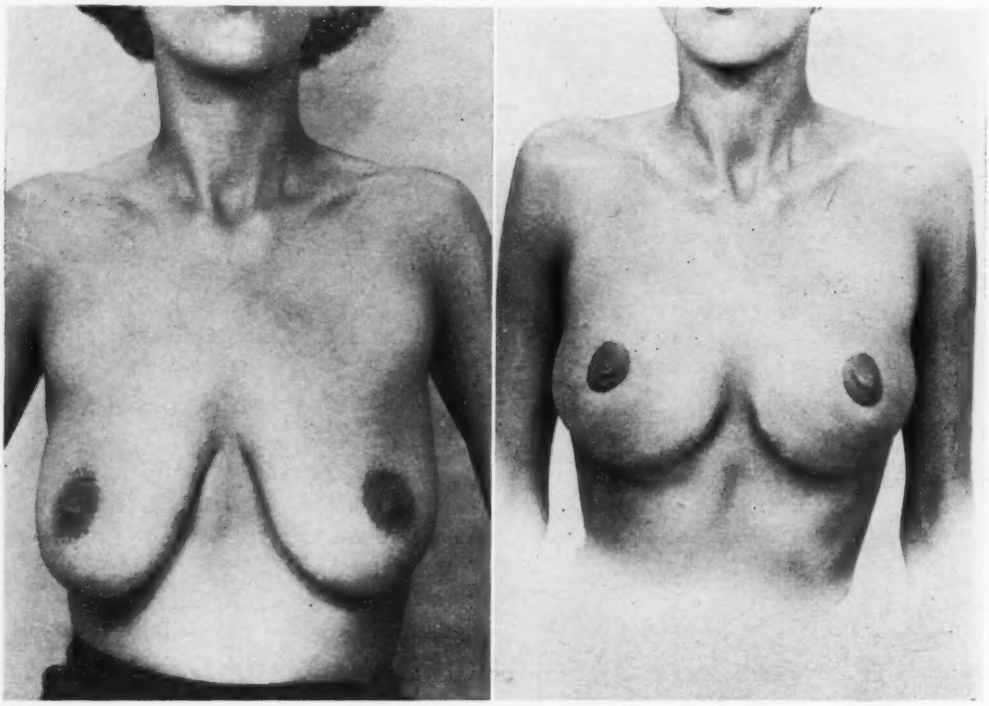


Fig. 1.—*One-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification:* *A* and *C*, Pendulous breasts with enlarged areola. The type of deformity and youth of the patient make this case ideal for the method. *B* and *D*, Symmetry of the breasts, the desired anteroposterior dimensions, the required areolar size, and the normal position of the nipple have been attained. The functional physiology is undisturbed. The inverted T-shaped scar blends with the breast contour.

fatty globules. Connective tissue surrounds each duct. The fibrous tissue also forms a support for the blood vessels, lymphatics, and parenchyma. In a lactating breast the gland structure enlarges; in turn the fibrous tissue stretches to accomodate the increase. There is a loss of fat and, consequently, a tendency for the breast to increase in size and become pendulous following this physiologic process.

EVALUATION OF THE DEFORMITY

Etiology.—Several factors may contribute to breast enlargement. Of these, heredity stands foremost. Pregnancy and lactation undoubtedly serve to distort breast contour. However, it is not uncommon to see many multiparae with one or even several children who have retained small contoured breasts.



A. *B.*

Fig. 2.—*One-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification: A,* Enlarged, asymmetrical breasts with the right breast extending 3½ cm. lower than the left. This type of asymmetry is not uncommon. *B,* The breast has been surgically reconstructed and the function retained.

Improper support may serve as an element in stimulating pendulous breasts. The binding brassière often acts to increase the ptosis. Lack of reasonable support during and after pregnancy may allow the breasts to prolapse premanently due to their excess weight.

Endocrine disturbances often lead to lax, pendulous mammary glands.[4]

Mechanism of the Deformity.—Many patients with hypertrophied, pendulous breasts present a history of steady gradual enlargement

dating from puberty. Those cases with small saclike dependent breasts usually elicit a history of their occurrence following pregnancy or excessive weight reduction. In these latter cases, there has been little absolute increase in fatty tissue, but rather an elongation of the glandular stalk,

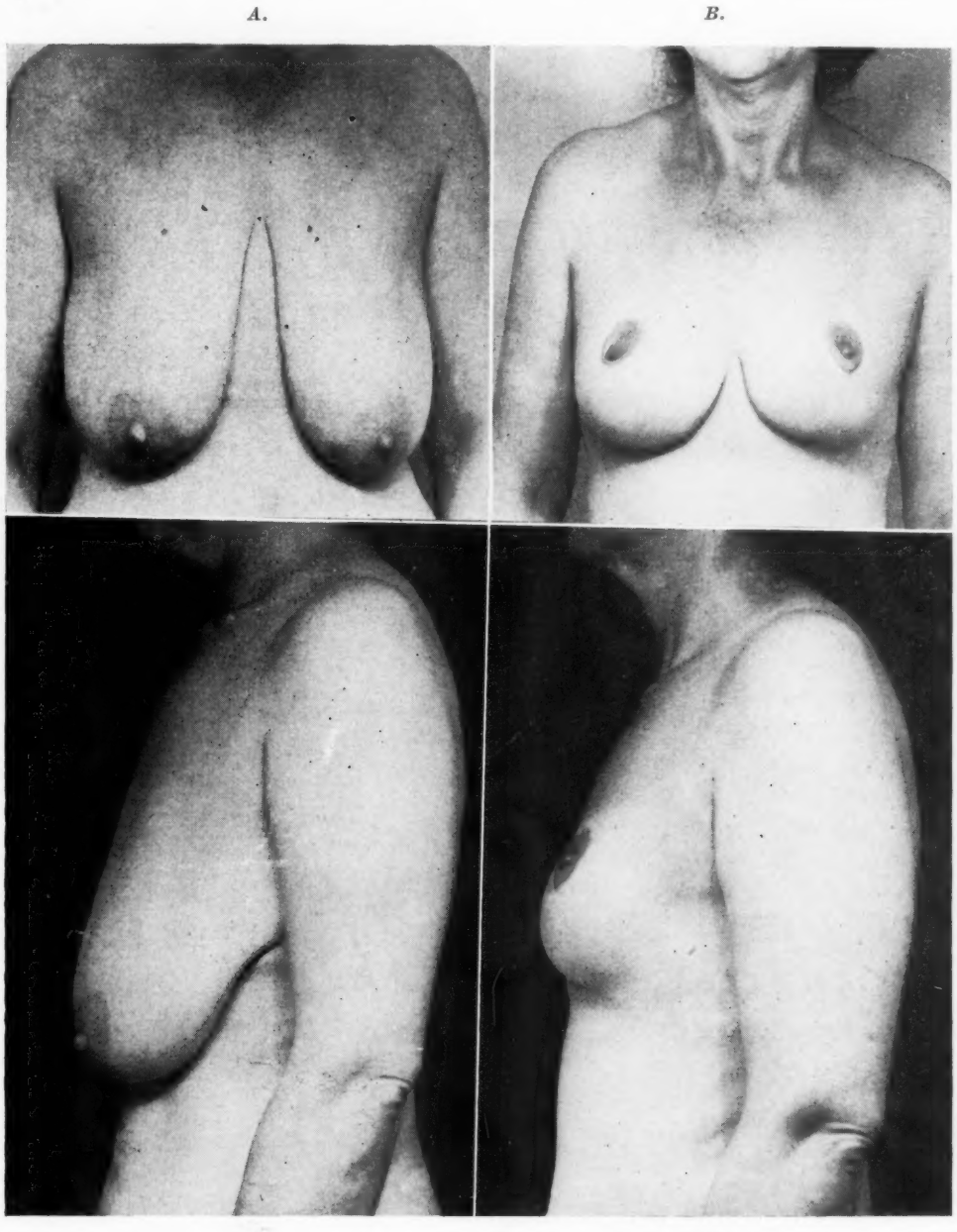


Fig. 3.—*One-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification: A* and *C,* Pendulous breasts with large areola. The patient presented poor posture, rounded shoulders, deep red shoulder strap marks, and great mental embarrassment. *B* and *D,* Patient returned to work in three weeks and photographs were taken six weeks after surgery.

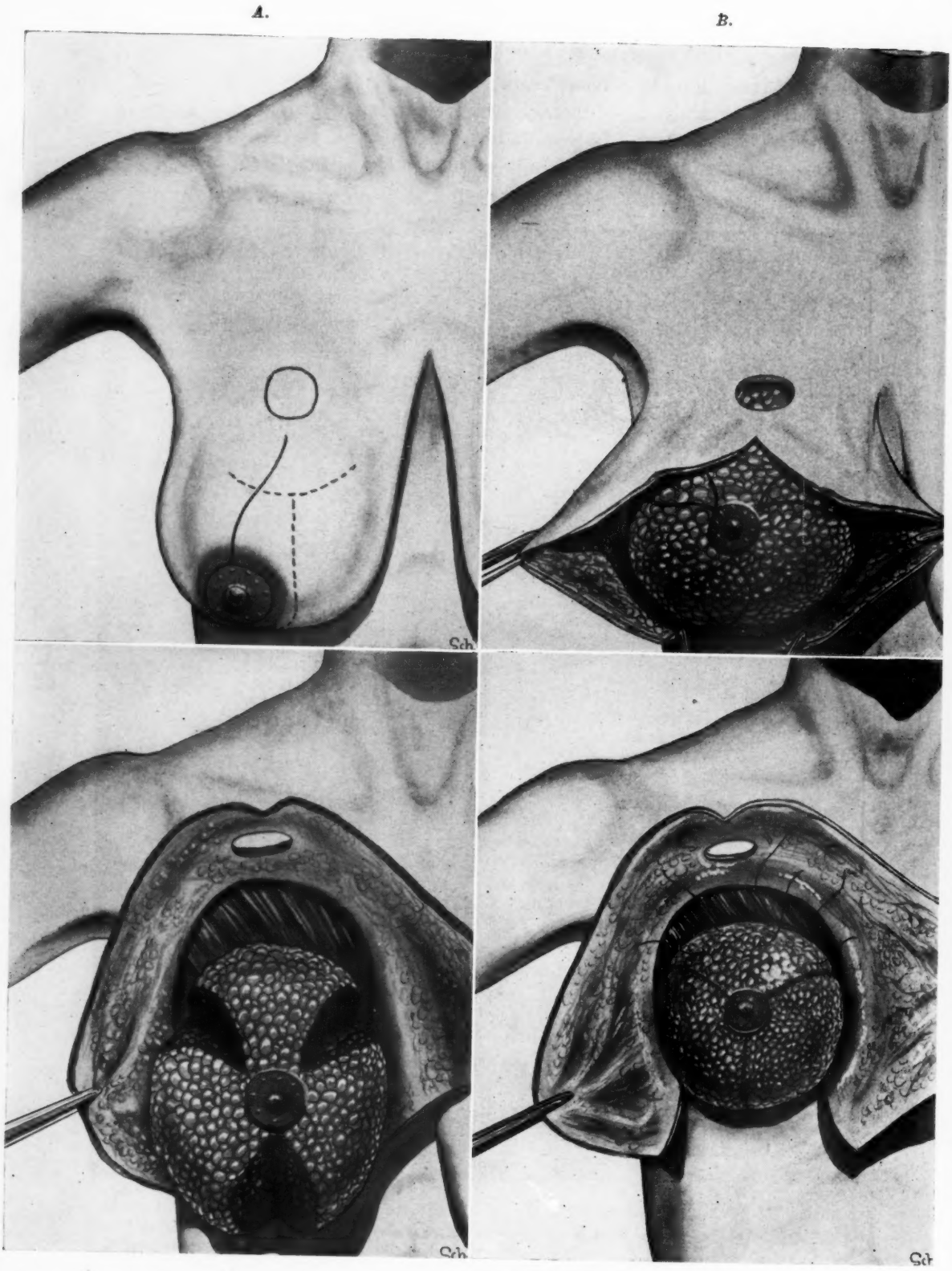
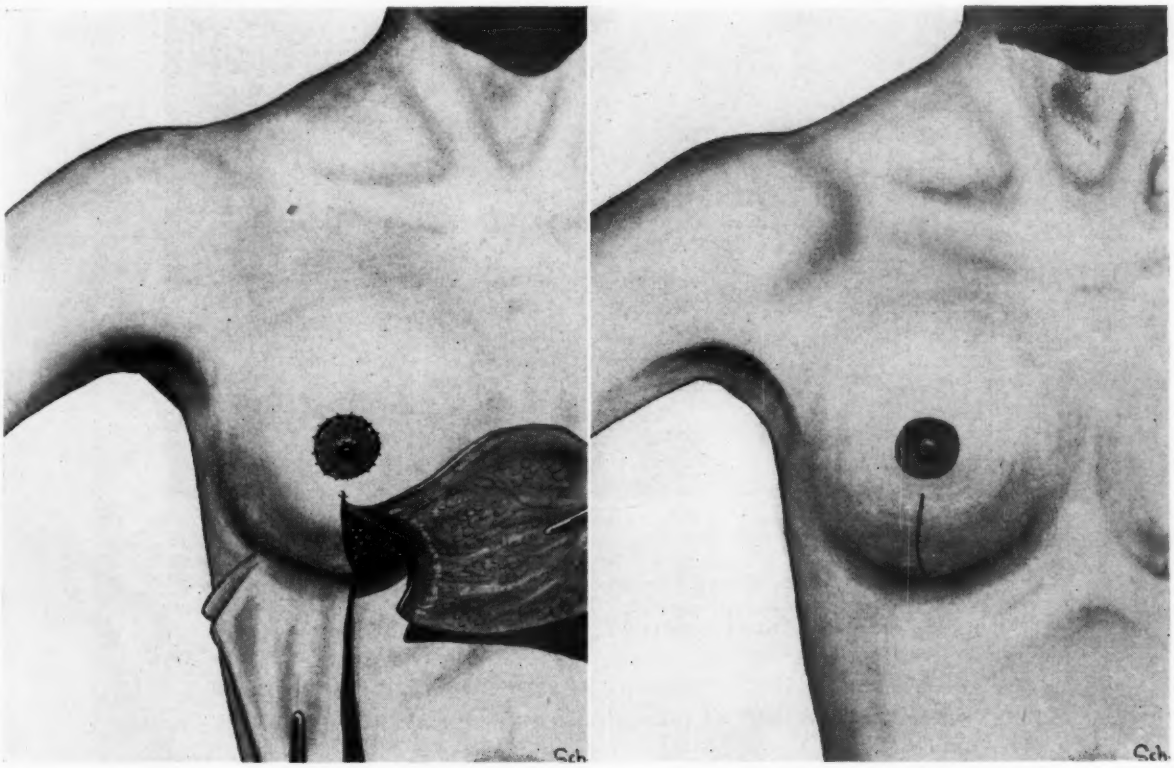


Fig. 4.—(*For legend see opposite page.*)

allowing the breast tissue to descend lower on the thorax with resultant stretching of the skin.

Measurements.—Numerous methods of gauging the new location of the nipple and breast have been evolved. These techniques have been well described[8] and the specific choice will depend upon the individual surgeon. Regardless of the procedure employed for measurements, the position of the nipple and breast will vary depending upon the size of the individual and the deformity encountered.

It is important to place the breast up to its theoretical position in order to gauge the new nipple location and the amount and areas of breast tissue to be removed. The reconstructed areola should not be created too small and its size should coincide with the newly constructed breast.



E. *F.*

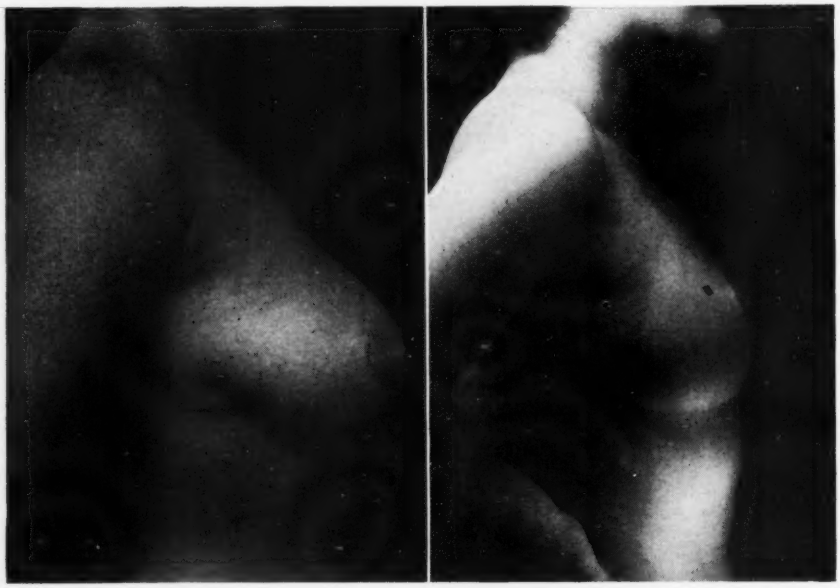
Fig. 4.—*Illustrations Depicting Author's Modification of the One-Stage Mastopexy: A,* The lines of incision have been carefully measured and marked, indicating the new position of the nipple, the amount of areola to be transferred, and the size of the skin flaps. *B,* The skin is undermined in a thick flap. The nipple and its required amount of areola are left attached to the completely denuded breast. Triangular wedges of tissue are marked off to be resected with respect to the circulation. A circular button of skin is excised to create the new nipple site. *C,* The wedges of breast tissue are resected, removing the required amount that will allow the reconstruction of a breast with the desired size, shape, and symmetry. *D,* The breast tissue is united with silk and the upper pole is fixed to the pectoral fascia over the second rib with heavy silk sutures. *E,* The areola is sewn into its new residence. The skin flaps are so cut as to adjust themselves to the new size, contour, and position of the breast. *F,* The wound edges of the inverted T incision are sewn with interrupted silk sutures.

Classification.—Gillies and McIndoe[5] have classified breast hypertrophies into the following types:

1. Long heavy pendulous breasts with hypertrophy of the most dependent glandular portion. This type probably is a resultant of both endocrine and congenital causes.

2. Broad, heavy breasts associated with obesity and exacerbated by pregnancy. This type, too, may be both endocrine and congenital.

3. Saclike dependent breasts which may follow obesity reduction, multiple pregnancies, or age.



A. *B.*

Fig. 5.—*One-Stage Mastopexy With Transposition of the Nipple . . . Author's Modification: A,* This patient, para iii, referred for surgery by her internist, suffered from mental embarrassment. *B,* This proved an ideal case for surgery, from both the standpoint of cooperation of the patient and the psychologic result.

4. True gynecomastia, with marked hypertrophy of the glandular elements of the breast resulting in enormous enlargement.

5. Asymmetry, which may vary from complete suppression of one breast to normalcy of one and excessive enlargement of its partner.

SURGICAL METHODS

During the last half century, various surgical procedures for mastopexy have been described. The evolution of surgical techniques has been classically reviewed by Thorek.[8] As the methods of procedure advanced, the operation for mastopexy developed from merely a removal of excess skin to a complete reconstruction of the breast. Until the last two decades, the method had one common defect. The breasts were

made somewhat smaller, but contour, symmetry, and shape were ignored. Often the procedures utilized were applicable for reconstruction of smaller breast deformities only. When large pendulous breasts were encountered with third degree ptosis, two and three stages were required and the results were often found wanting.

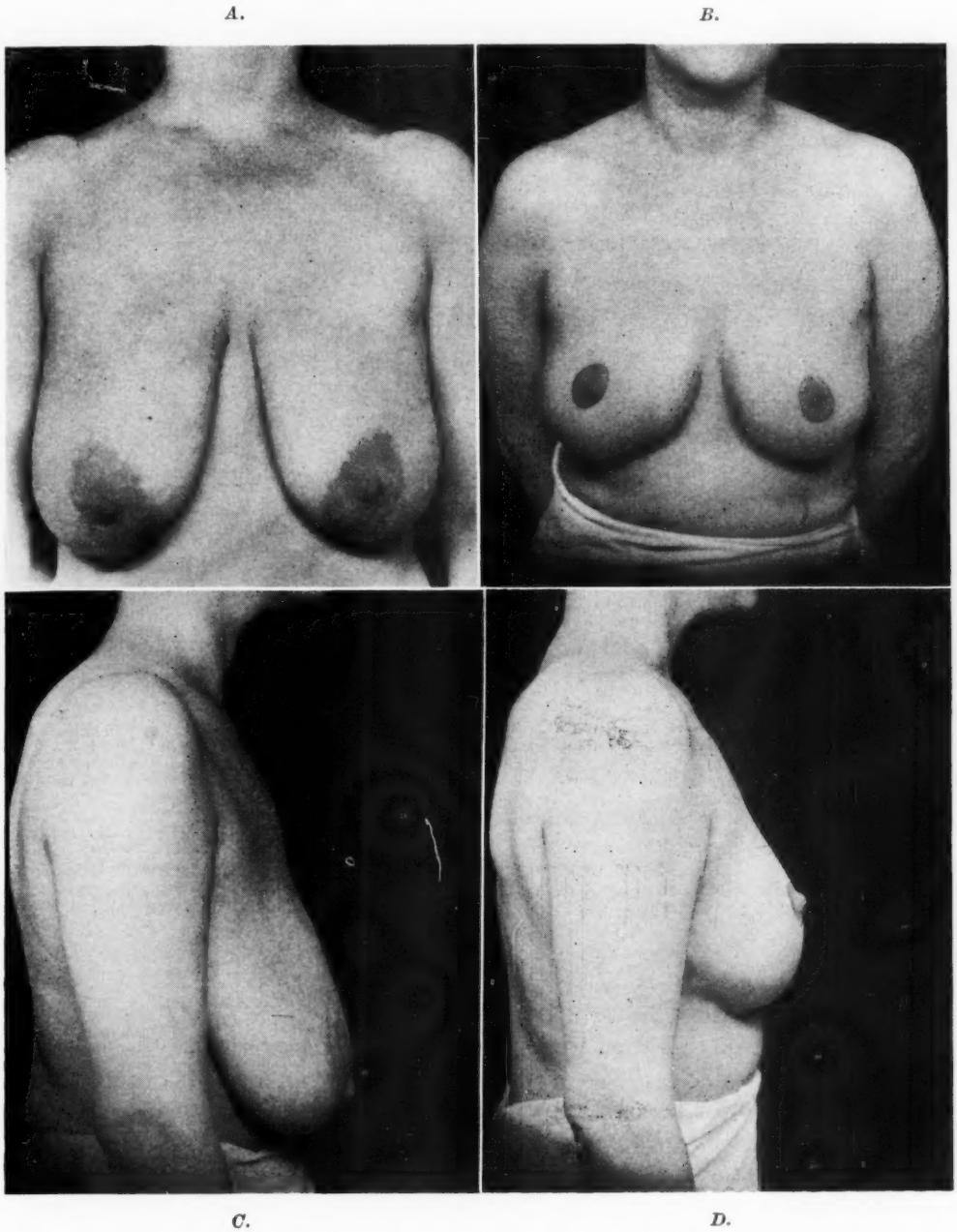
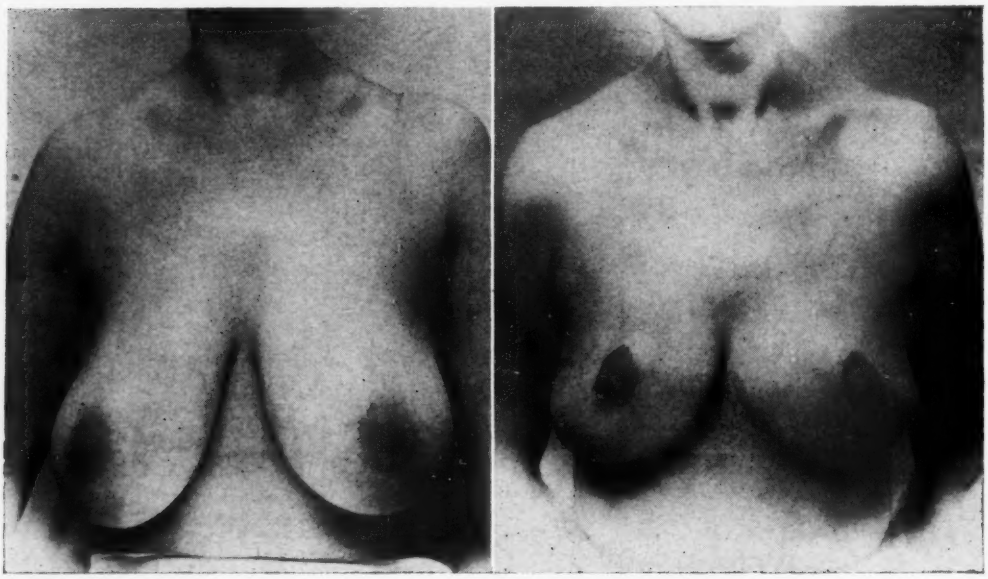


Fig. 6.—*One-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification: A* and *C,* Enlarged asymmetrical breasts associated with poor posture and marked physical discomfort; para i, with functional breasts. *B* and *D,* Reconstruction of the breasts and transposition of the areola with retention of physiologic function. Patient has recently had a second child.

We believe that no single surgical method should be applied to all cases, but rather the surgeon should vary the approach with the existing deformity.

We divide the surgical methods into three categories:

1. *One-Stage Mastopexy With Transposition of the Nipple:* Modified after Joseph, Lexer, Kraske, Noel, Beisenberger, Schwartzman, Gillies, and McIndoe. (Figs. 1 through 9.)
2. *Two-Stage Mastopexy With Nipple Transplant:* Modified after Thorek and Updegraff. (Figs. 10 through 13.)
3. *Two-Stage Mastopexy With Transposition of the Nipple:* Modified after Morestin, Villandre, Lotsch, Passot, Axenhausen, and Defermontel. (Figs. 14 through 16.)



A. *B.*

Fig. 7.—*One-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification: A,* Pendulous hypertrophied breasts with excess fatty tissue causing physical debilitation. *B,* The scars following surgery are longer in this case because of the initially large breasts.

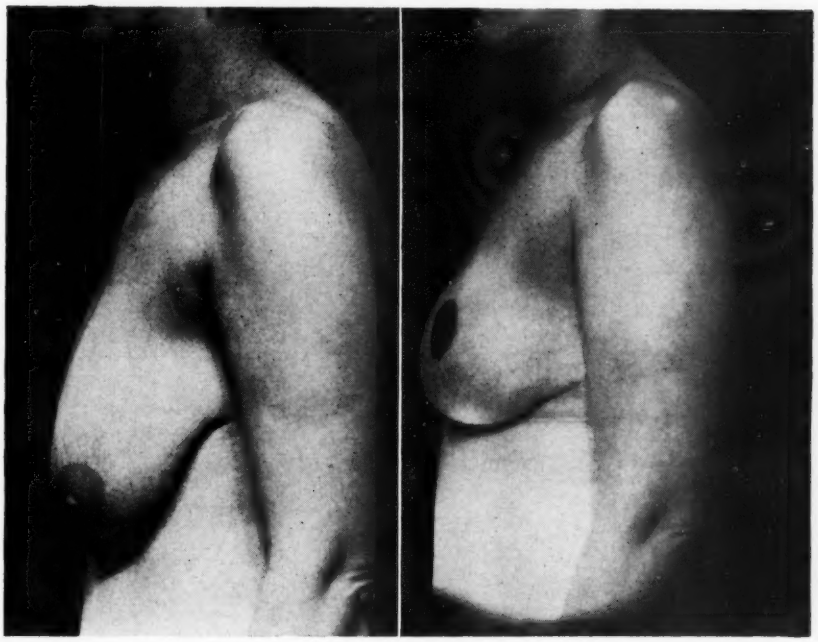
SURGICAL TECHNIQUE

One-Stage Mastopexy With Transposition of the Nipple

The one-stage operation with transposition of the nipple may be used in the majority of patients with enlarged, hypertrophied breasts. The method allows for breast reconstruction with the desired symmetry, size, and shape in conjunction with retention of its functional physiology.

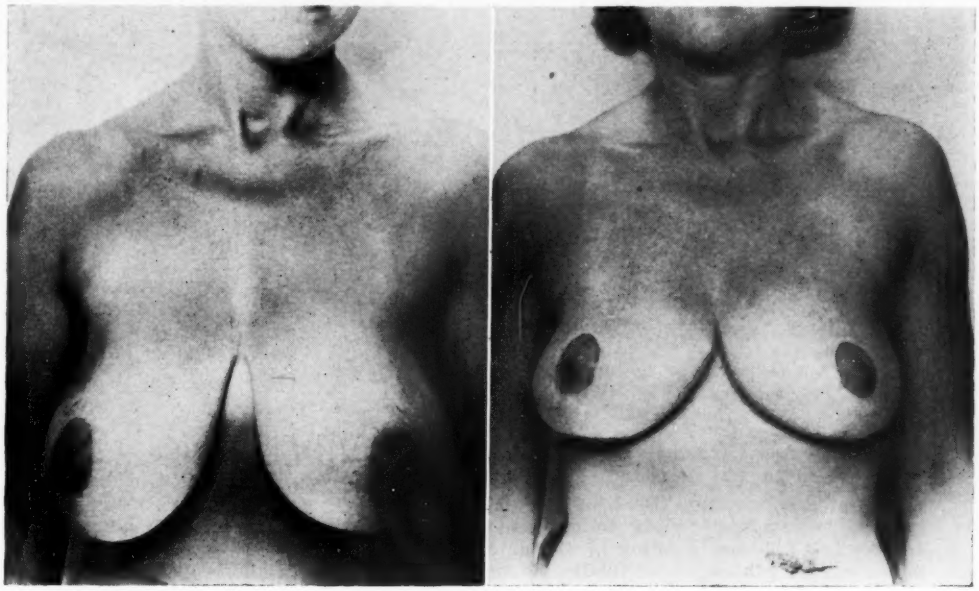
Author's Modification.—The patient is placed on the table in a semi-Fowler position with the arms akimbo. The anesthesia is usually intratracheal.

The lines of incision which have been carefully measured and marked the previous day are remarked. The initial incision is circular around the areola. From the center edge of this incision another is made



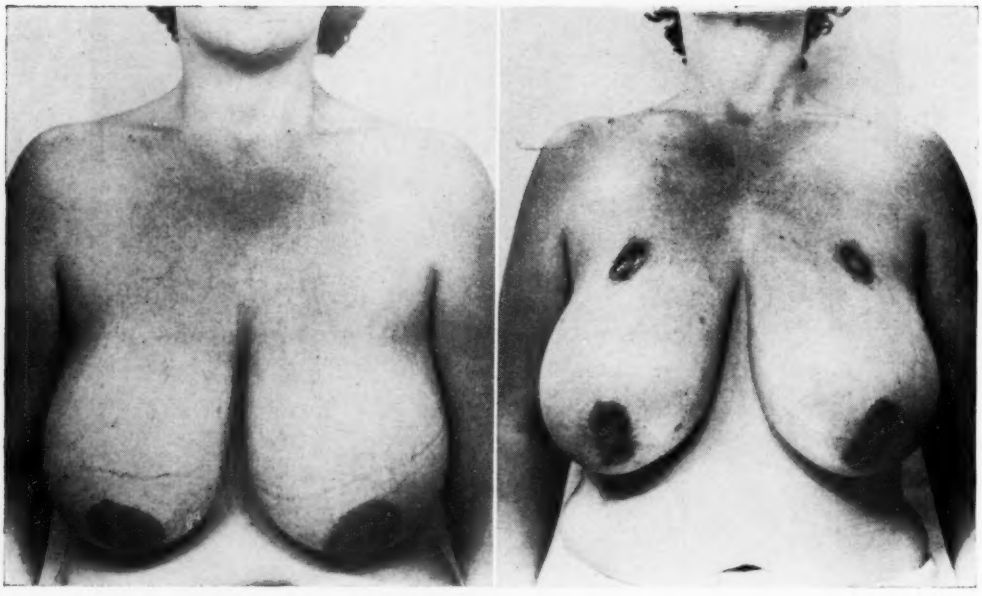
A. *B.*

Fig. 8.—*One-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification:* A, Long, heavy, pendulous breasts in a younger woman, probably of congenital and endocrine origin. The ptosis resulted in mental and physical discomfort. *B,* Surgical reconstruction with the cross of the inverted T incision well concealed by the normal position of the lower pole of the breast, while the handle of the incision may be seen running from the areola downward.

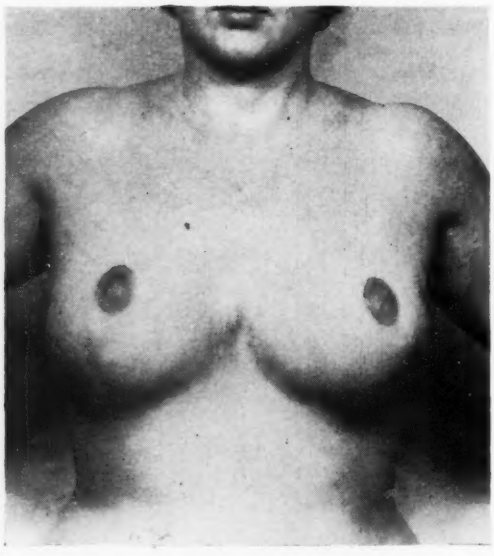


A. *B.*

Fig. 9.—*One-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification: A,* Because of the marked hypertrophy, this case may have lent itself better to a two-staged operation. *B,* The one-stage procedure proved quite satisfactory.

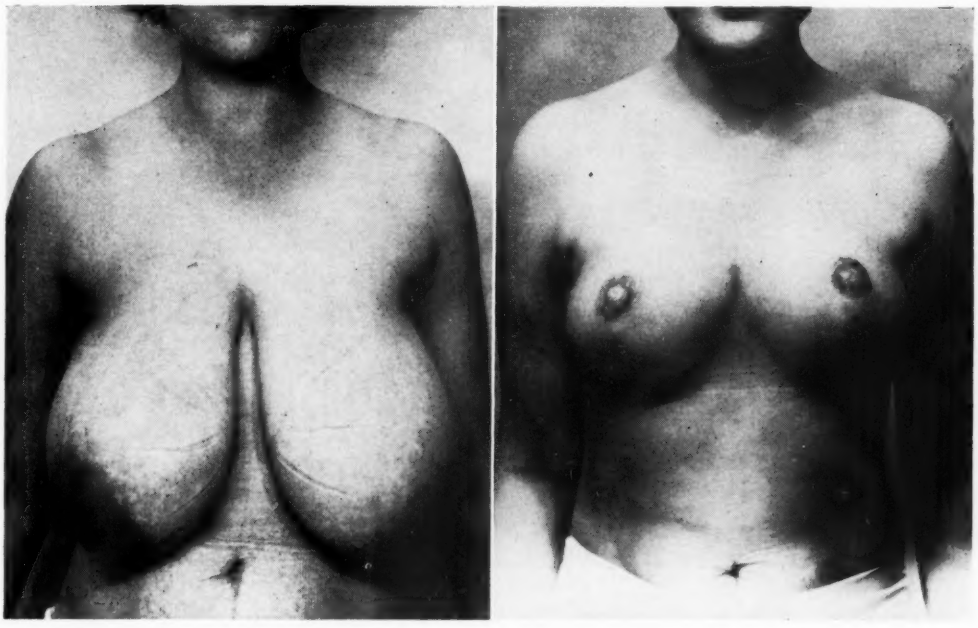


A. *B.*



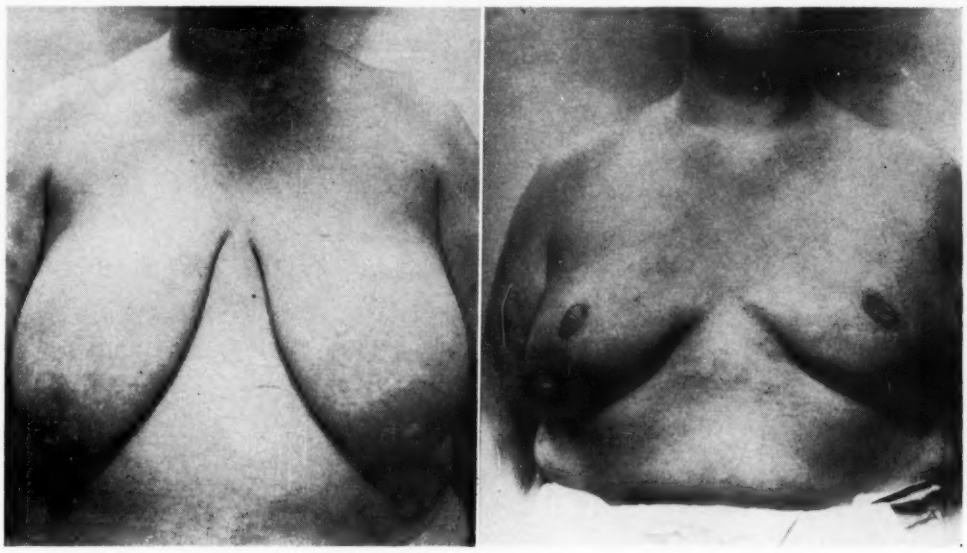
C.

Fig. 10.—*Two-Stage Mastopexy With Nipple Transplant. . . . Author's Modification After Thorek: A,* Marked hypertrophy associated with a nonfunctional breast necessitated a two-stage operation. The surgeon's discretion is used in choosing the type of two-stage operation to be employed. *B,* Following careful measurements to ascertain the new position of the nipple and the desired size, contour, and symmetry of the contemplated breast, the former is transplanted to its new residence. *C,* Two weeks afterward, the required amount of breast tissue is resected by removing triangular wedges. The skin flaps are adjusted, the wound edges are approximated in the form of an inverted T and sewed with interrupted silk sutures.



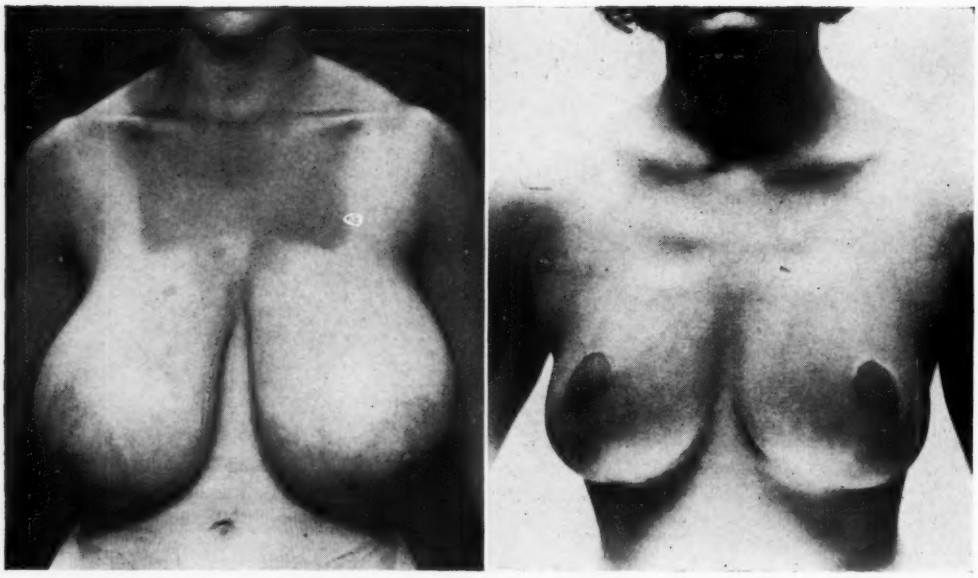
A. *B.*

Fig. 11.—*Two-Stage Mastopexy With Nipple Transplant. . . . Author's Modification After Thorex:* *A,* Generalized breast hypertrophy in a young girl associated with nonfunction. The conditions present required two-stage operation for reconstruction. *B,* Two months following the second stage operation: the nipple transplants have taken well and the breasts have been reconstructed to the required size, shape, and symmetry.



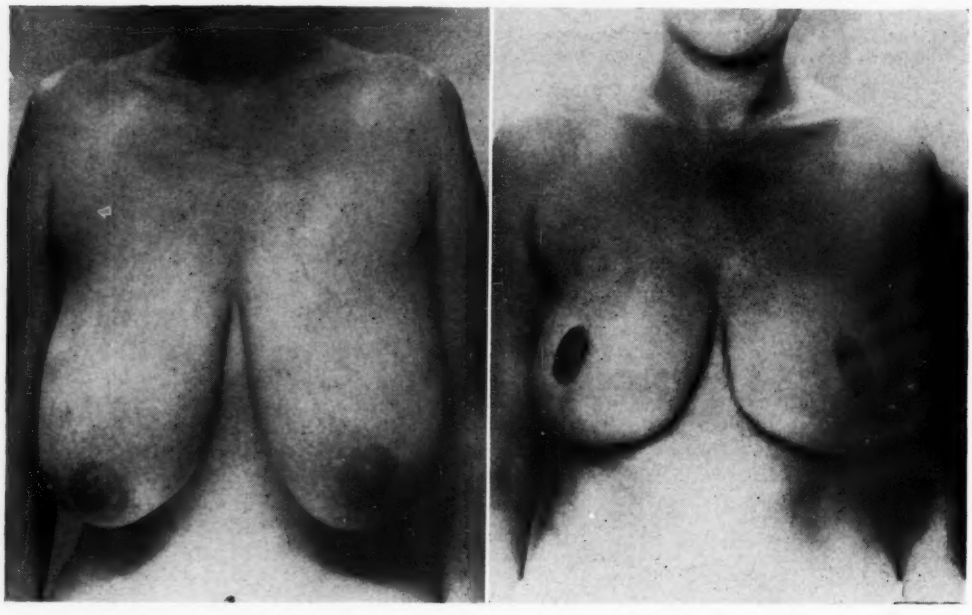
A. *B.*

Fig. 12.—*Two-Stage Mastopexy With Nipple Transplant. . . . Author's Modification After Thorek:* *A,* Nonfunctional markedly hypertrophied breasts causing the patient great physical discomfort. *B,* The nipple was transplanted on either breast, and two weeks later the required amount of breast tissue was resected.



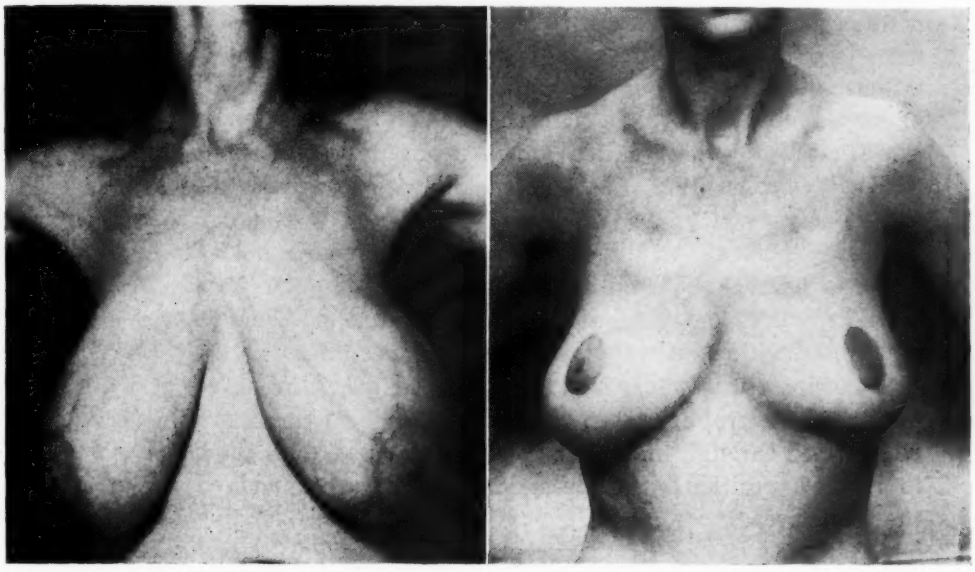
A. *B.*

Fig. 13.—*Two-Stage Mastopexy With Nipple Transplant. . . . Author's Modification After Thorek: A,* Pendulous nonfunctional breasts in a younger girl. *B,* Photographs taken four months afterward, demonstrating the surgical result.



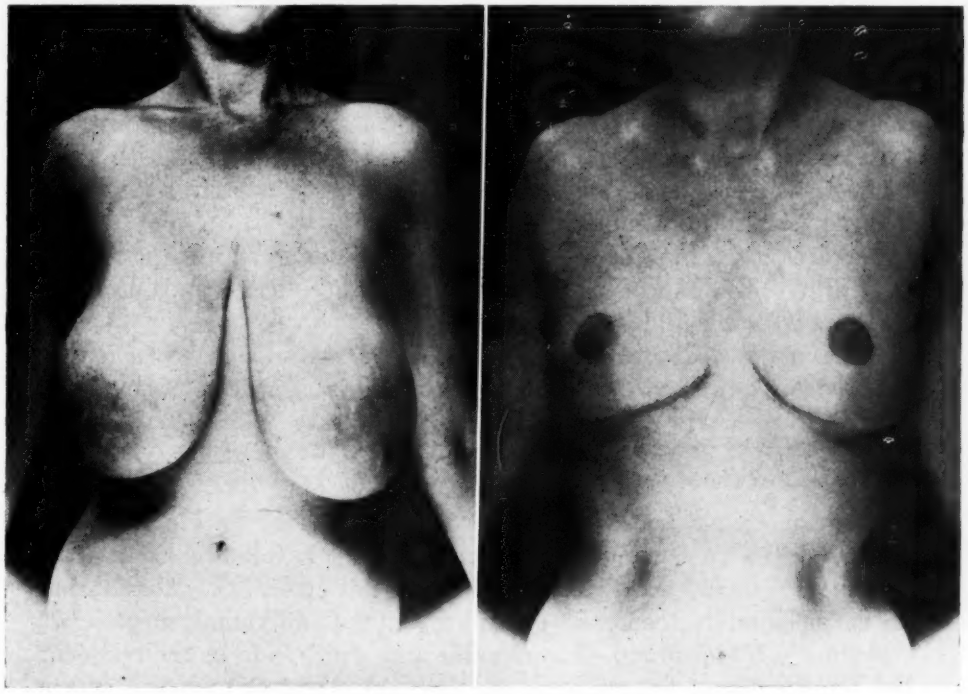
A. *B.*

Fig. 14.—*Two-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification: A,* The nipple with its areola attached to the partially denuded breast is transferred to its new position. The upper pole is fixed to pectoral fascia with silk. A fortnight afterward, the required amount of breast tissue is resected by excising triangular wedges. The skin flaps are cut, adjusted, then approximated with silk to form an inverted T. *B,* Photographs taken three months following the second stage operation.



A. *B.*

Fig. 15.—*Two-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification:* *A,* The weight of the breasts caused the patient great physical discomfort. These breasts were functionless and ideal for a two-stage operation. *B,* Two and one-half months following surgery.



A. *B.*

Fig. 16.—*Two-Stage Mastopexy With Transposition of the Nipple. . . . Author's Modification:* *A,* Markedly hypertrophied, asymmetrical breasts requiring reconstruction. *B,* Six weeks following surgery.

perpendicularly upward to the new nipple site. The skin of the breast is undermined in a thick flap and the plane of cleavage located. Trauma must be avoided; gentleness is primary or a loss of skin flap may occur. Oftentimes, the skin may be peeled away from the tissue with the aid of a sponge, while in some cases careful spreading with a scissors in the line of cleavage will gain the required result.

The breast, entirely denuded of skin with its nipple and areola attached, is pushed up to the desired position on the chest. This allows the surgeon an opportunity to evaluate the amount and area of breast tissue to be removed. Either two or three triangular wedges of tissue extending down to the pectoral fascia are resected. The areas are closed by approximating the walls with silk sutures.

Following satisfactory reconstruction of the breast proper, three heavy silk sutures are taken through the pectoral fascia over the second rib, carried through the upper poles of the breast, and the latter is fixed to its new position. Sulfanilamide crystals are sprinkled throughout the whole area.

A circular button of skin previously marked to serve as the new location for the areola and nipple is now removed. The skin flaps from either side are brought around the breast, meeting in the center where the excess is excised (Fig. 4 *E*). The subcutaneous tissue is approximated and the skin closed with interrupted silk sutures. A Penrose drain is inserted beneath the flaps through either corner of the lower incision.

The opposite breast is similarly reconstructed. Care is taken to create symmetry and similarity between the two breasts. If the decision is to place one nipple slightly lateral, then the other must be placed in a comparable location. It requires more time and effort to reconstruct two nearly identical breasts, both of desirable shape, position, and symmetry. However, a pleasing end result always compensates the surgeon for his thoroughness.

The dressing is applied: parresine mesh impregnated with petroleum jelly over the wound edges, gauze flats over the breasts, and moderate pressure with a stockinet bandage.

Some of the silk sutures are removed at the end of the sixth day, the remainder on the eighth day. The brassière is adjusted and used for support as the swelling subsides.

Two-Stage Mastopexy With Nipple Transplant

Oftentimes in a markedly enlarged breast, it may be the surgeon's opinion that a two-stage operation with nipple transplant is the method of choice. Thorek[9] was the first to describe this operation. Modification of his original method will depend upon the individual surgeon.[1, 10]

Author's Modification.—The circular area which is to be the recipient bed for the nipple transplant is carefully measured and marked with a 3 per cent gentian violet solution. Following this circle, an incision is made through part of the derma and the skin is dissected free leaving a bed for the reception of the nipple and its areola. All bleeding is controlled.

An incision is made around the areola following a previously marked circle, and the structure is dissected free almost as a full-thickness graft. The nipple with its areola is transferred to its recipient bed and sewed in place with interrupted fine silk sutures.

A similar procedure is followed on the opposite breast. A suitable pressure dressing is applied. The sutures are removed about the tenth day when pressure is reapplied and the area is treated similar to a full-thickness graft.

Second Stage.—After two weeks, the secondary procedure is carried out under general anesthesia. An incision is made from the center of the nipple downward; another is run along the undersurface of the breast (Fig. 4 *A*). Two thick skin flaps are created similar to the method in the one-stage mastopexy. The required amount of breast tissue is resected in the form of triangular wedges. The walls are approximated with silk and sulfanilamide crystals sprinkled over the area.

The skin flaps are cut and approximated in the shape of an inverted T. This allows for the reconstruction of a more shapely breast with the desired anteroposterior dimensions and conical symmetry. The inframammary scar is virtually hidden by the lower pole of the breast, while the handle of the inverted T shaped scar is not too noticeable.

Two-Stage Mastopexy With Transposition of the Nipple

This operation is applicable to excessively large breasts that have hypertrophied and retained an abundance of fatty tissue. An attempt to reconstruct a breast of this type to a normal size in a one-stage operation will usually result in necrosis of the nipple and a bizarre breast contour. Or it may result in a breast that is only slightly smaller with its pendulousness retained but now added to it, surgical scars.

Author's Modification.—Under general anesthesia an incision is made around the areola retaining the desired amount for transfer. From the center of the upper edge of this circle, an incision is carried perpendicularly upward to within one-half inch of the new nipple site. From the lower center of the circle an incision is carried perpendicularly downward to the inframammary line. Another incision, some four inches long, is carried around the inframammary line forming an inverted T. Either one or two triangular wedges of breast tissue are taken from the upper pole and the walls approximated. The skin over the breast is undermined in a thick flap to an area just below the clavicle. The upper pole of the breast is fixed at three points, with heavy silk sutures, to the pectoral fascia over the second rib.

A circular area of skin having been previously marked as the new nipple site is excised, and the nipple with its areola is carefully sewed into its new residence. Sulfanilamide crystals are sprinkled into the wound. The excess amount of skin from the apron flap is removed with a semicircular incision and the edge sewed to the lower skin flap with interrupted silk sutures. A Penrose drain is inserted high into either corner of the wound.

A similar procedure is performed on the opposite side. Moderate pressure and support are applied with a stockinet bandage.

Second Stage. A fortnight later, the nipple having gained sufficient circulatory support in its new residence, the patient is again submitted to surgery.

The previous line of incision along the inframammary region is opened and from its center an incision is made upward to the center edge of the nipple forming an inverted T. Two thick triangular flaps are then created by undermining, thus exposing the right and left poles of the breast. Depending upon the amount of breast tissue to be removed, either two or three triangular-shaped wedges are taken, and if necessary a semicircular section is removed along the inframammary region. The walls are approximated with silk.

The required amount of skin is removed both from the center of either flap and from its inferior portion. The wound edges are approximated subcutaneously and the skin is sewed with interrupted silk sutures. A Penrose drain is placed in either angle of the wound.

A similar procedure is repeated on the opposite side with care and effort expended to create both breasts of equal size and shape and at the same time conical with the required anteroposterior dimensions. Suitable pressure dressing is applied.

SUMMARY

Enlarged and pendulous breasts usually may be reconstructed in a one-stage operation. This procedure allows for both breasts to be virtually identical and to retain their physiologic function. The author's modification of this method permits the breasts to be reconstructed to the desired size, shape, and contour and results in smaller postoperative scars.

In some cases, depending upon the judgment of the surgeon, a two-stage operation may be required. Either transposition or transplantation of the nipple may be employed at his discretion.

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TREATMENT OF PUBERTAL BILATERAL GYNECOMASTIA

Report of a Case

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INTRODUCTION

SINCE diffuse enlargement of the breast in the male unassociated with tumors of the genital system occurs with some frequency and has been a source of much debate, we were led to study in some detail a case of bilateral hyertrophy in a 16-year-old boy.

On a histologic basis a number of workers[1, 2] have classified enlargements unassociated with malignant tumors into two classes, true gynecomastia and pseudogynecomastia. The first shows proliferation of ducts and periductal connective tissue, while the second shows normal male breast tissue and is presumed to be due to localized fat deposits or to overgrowth of fibrous connective tissue following injury (chronic fibrous mastitis). Any relation of these to endocrine disorders has been questioned.

In favor of endocrine participation is the fact that many of the enlargements occur when the male is at the age of puberty or soon thereafter, without a history of trauma. In many cases some phases of puberty have been delayed. And in a number of instances considerable reduction in the size of the breast has followed the prolonged administration of androgens.[3, 4]

The group of cases described by Klinefelter, Reifenstein, and Albright[5] showed bilateral enlargement of the breasts associated with small testes, aspermatogenesis, and little growth of facial hair. There was a normal growth of pubic hair and external genitals. The excretion of 17-ketosteroids was normal to definitely subnormal. In the two cases tested, the estrogen secretion was normal. They report no benefit from administration of androgens.

The case to be described is that of a 16-year-old young man with bilateral gynecomastia developing at puberty. In many respects he resembled the cases described by Klinefelter and his associates. The quantitative changes in volume of the breasts and the 17-ketosteroid excretion were followed during a period of intensive therapy with testosterone.

This work was aided by a grant from the Graduate Research Fund, University of Minnesota.

Received for publication Aug. 28, 1944.

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CASE HISTORY

Past History.—A 16-year-old, unmarried, white, male student had noticed gradual increase in the size of both breasts for two years, associated with breast pain. Except for scarlet fever at the age of 10, his general health had been excellent. Past history was noncontributory. Development had been normal, voice changing at the age of 14 years. He had experienced erections, nocturnal emissions, and sexual intercourse with ejaculations.

Examination.—The patient was a tall, asthenic individual. He measured 69 inches in height and weighed 143 pounds. Increased adiposity was noticed about the mammae and trochanteric areas. There was no beard, although fine dark hair was present on the upper lip. The axillary hair was sparse, the pubic hair was abundant but with the female escutcheon. There was virtually no hair on the trunk or extremities. The carrying angle was increased. The skin was soft, smooth, somewhat dry, with a minimum of oiliness. The facial appearance was boyish, demeanor unassuming; the voice was low in pitch and masculine. The thyroid cartilage was not prominent.

The breasts were symmetrically enlarged, with the consistency, size, and configuration of a well-developed adolescent female. The nipples were moderately retracted with a dark areolar pigmentation. No discharge was obtained from either nipple. The chest measured 35 inches around the nipple line.

He complained of a sense of fatigue and narcolepsy. The external genitals were well developed. The seminal vesicles were not palpable and the prostate was very small.

Laboratory Data.—The Kahn and Wassermann tests were negative. Studies of the urine and blood were within normal limits. Blood cholesterol was 158 mg. per 100 c.c., the basal metabolic rate was −7 and −2 per cent, bleeding time (ear) 3½ minutes, clotting time (ear) 2½ minutes. Plasma proteins were normal, prothrombin time 19.4 minutes (control 19.2). Serum phosphatase was: acid 9.9, alkaline 10.2 mg. Hippuric acid and cephalin-cholesterol tests were within the normal limits. Sperm counts on two occasions were found to be 2,200,000 per c.c. Of the sperm present, only 25 per cent showed motility and normal morphology.

Roentgen Reports.—The following roentgen report was submitted:*

Aug. 7, 1942, Skull: The skull appeared entirely normal except for some sclerosis of the mastoids. The sella turcica appeared normal. Conclusions: Negative skull and sella turcica; sclerotic mastoid.

Aug. 25, 1942, Pneumo-adrenogram: There was a good insufflation of air about the left kidney and in the left adrenal space. On the right side, the insufflation was less satisfactory as the air was injected somewhat lower down. The left adrenal was clearly made out, but I believe it was within normal limits. Conclusion: Probably negative adrenal.

Sept. 8, 1942, Pathology: There was no evidence of pathology in the lungs, mediastinum, diaphragm, or pleura. The heart appeared normal. Conclusions: negative.

Sept. 18, 1942, Examination: Simple examination of the urinary tract showed no evidence of abnormality. The epiphyses for the crest of the ilia would indicate some slight advance in ossification although this is probably of the upper limits for the age of 16. The epiphyses of the spine were within normal limits in their degree of development.

Course of Therapy.—October, 1942, six injections of 1 c.c. of antuitrin compound were given at weekly intervals without any apparent effect in arresting the mammary development.

Two series of twenty-four hour collections of urine were analyzed for 17-ketosteroids and estrogens; one before any treatment and one during ineffective gonado-

*Report of Dr. Leo Rigler, roentgenologist at the University Hospitals.

trophic administration (Table I). The average excretion of 17-ketosteroids was 5.8 mg. in twenty-four hours, a value below that which we have obtained in normal young men (9 to 20 mg. in 24 hours). The estrogen level (9 to 26 I.U.), on the other hand, was well within the normal range.

TABLE I

ESTROGEN ACID 17-KETOSTEROID EXCRETION

SAMPLE NO.	COLLECTION PERIOD (IN HR.)	DATE		URINE VOL. (IN C.C.)	ESTROGENS I.U. PER 24 HR.	17-KETOSTEROIDS MG. PER 24 HR.
1	24	8/13/42		1770	7.8	6.1
2	24	8/14/42		1080		4.9
3	24	8/15/42		1950	9.0	6.4
4	24	8/16/42	Discarded	1420		
5	24	10/11/42	After gonadotrophic hormone	1680	21.0	6.2
6	12	10/14/42	After gonadotrophic hormone	765		5.8
7	12	10/15/42	After gonadotrophic hormone	725	11.0	7.4
8	12	1/14/43		650	15.0	7.0
9	12	1/13/43		680		7.1
10	12	1/15/43		900		4.8?
11	12	3/17/43	Testosterone propionate 25 mg. per day	530	>11	10.8?
12	?	3/18/43	Testosterone propionate 25 mg. per day	1140		17.5
13	?	3/19/43	Testosterone propionate 25 mg. per day	610		11.8
14	9	4/14/43		360		5.8
15	13	4/15/43		260	10.0	4.7
16	13	4/16/43		650		8.0
17	24	4/21/43		950		1.5
18	24	4/23/43		580		3.1

Since there was some evidence of a decrease in the 17-ketosteroids, to which the naturally excreted androgens belong, an intensive course of androgen therapy was tried. Intramuscular injections of 25 mg. testosterone propionate* were administered daily for fifty days.

The following changes were observed during the intensive course of replacement therapy. The prostate increased in size, but remained small, and the seminal vesicles became palpable. There was no increase in libido or in nocturnal emissions. Sense of well-being and energy improved, although the narcolepsy increased but later improved. The previous unassuming attitude changed to one which was more aggressive. Facies became more mature. Acne did not appear on the face but was noticed on the shoulders and arms. The increase in sebaceous secretion and ruddiness developed in the face. The voice became rough and deeper pitched. There was an easily discernible increase in the size of the skeletal muscles, especially about the shoulder girdle and an increase in height of 1½ inches. The patient noticed increased strength and improvement in psychologic outlook.

The effectiveness of the therapy is indicated by the increase in the excretion of 17-ketosteroids as shown in Table I. There was no evidence of drug toxicity. The breasts appeared to decrease slowly in size during this treatment. This was

*The testosterone propionate was furnished by Ciba, Pharmaceutical Products Inc., Summit, N. J.

TABLE II

VOLUME OF CASTS OF BREASTS MEASURED FROM GENERAL LEVEL OF BODY WALL

11/20/42	Right breast	Before testosterone	62 c.c.
11/20/42	Left breast	Before testosterone	56 c.c.
1/ 8/43	Right breast	Before testosterone	60 c.c.
1/ 8/43	Left breast	Before testosterone	53 c.c.
4/17/43	Right breast	After testosterone but before surgery	28.5 c.c.
4/17/43	Left breast	After testosterone but before surgery	27.0 c.c.
6/13/43	Right breast	After surgery	10.5 c.c.
6/13/43	Left breast	After surgery	9.0 c.c.

confirmed by a comparison of plaster casts made before and after treatment. The change in volume measured beyond the general level of the chest wall is given in Table II. The relative changes in contour are indicated in Fig. 1, where the outlines of the plaster casts at the same point are given before and after testosterone and after surgery. The individual contours were flattened during the application of the casts so that the true outline of the breast is not represented.

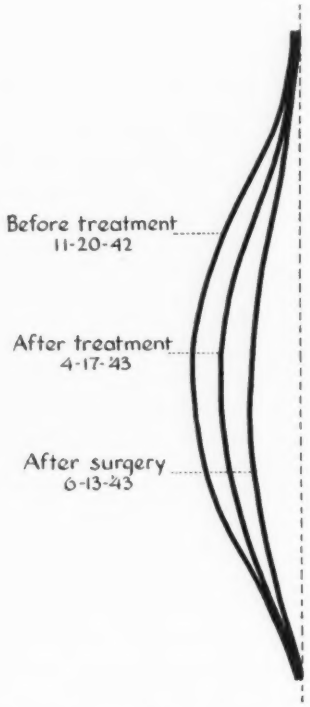


Fig. 1.—Vertical contour of casts of right breast taken at nipple line. (One-half actual size.)

There was a decrease in the size of the breasts while testosterone propionate was being injected, but it was felt that the improvement was too slow and the treatment too expensive to be of any practical value. Bilateral mastectomy with preservation of the nipples was therefore performed; the result obtained can be seen in Fig. 2. The change in volume and contour are given in Table II and Fig. 1.

Fig. 3 illustrates the gross appearance of the masses removed. The pathologic report was as follows:

Pathologic Examination.—The specimens consisted of two discoid masses weighing 115 and 125 Gm. and measuring 8.5 by 7 by 3 cm. and 11 by 7 by 3.5 cm.,

respectively. These specimens externally and on section were composed of uniformly white, rubbery, hard tissue. No cysts were seen. No adipose tissue was present on the cut surfaces.

Microscopic Examination.—Sections from two areas in each specimen showed that the tissue was predominantly fibrous tissue, part of which was hyaline (Fig. 3). Almost no leucocytes were present. Very few blood vessels were seen. Scattered through each section were a few ducts but no lobules. An occasional duct showed branching. Most of the ducts were lined with two or three layers of cuboidal cells. No mitotic figures were observed nor was necrosis noted. The appearances were interpreted as being those of chronic fibrous mastitis.

Comparison of these sections with those from twelve instances of unilateral chronic fibrous mastitis in males, ranging in age from 13 to 67 years of age, showed almost identical appearance in all. The present instance differed from the other twelve only in the fact that it contained fewer ducts than any of the others. All showed practically identical appearance of the fibrous tissue except for the degrees of hyalinization. None showed any appreciable leucocytic infiltration or vascularity. A few showed a little suggestion of lobulation. One showed a single duct containing a few papillary projections of its epithelium.

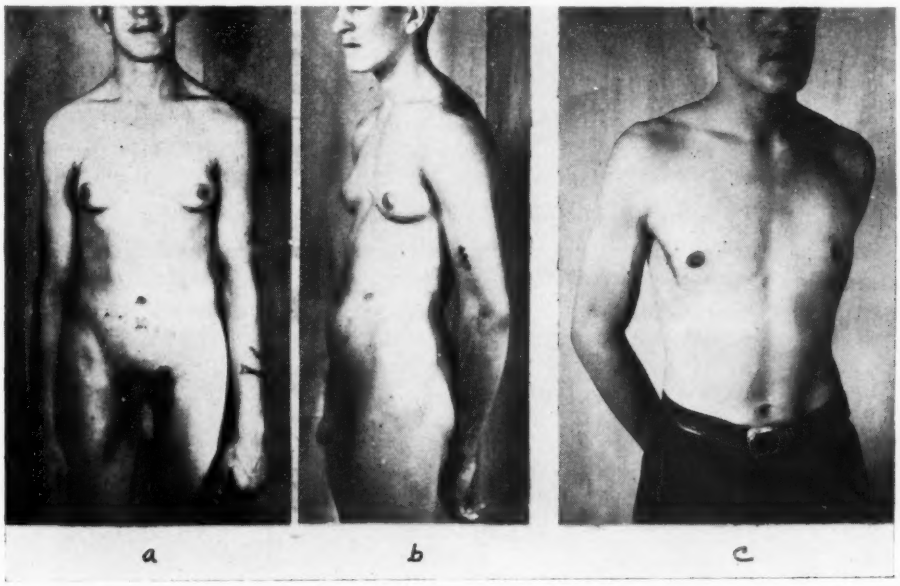


Fig. 2.—Appearance of patient before and after bilateral mastectomy. Photographs *a* and *b* were taken before treatment of any sort was given. Photograph *c* was taken after mastectomy.

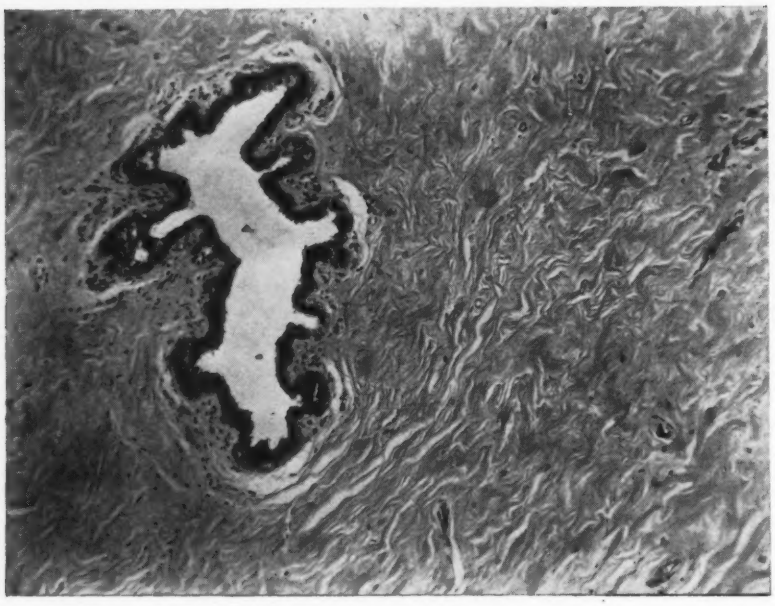
DISCUSSION

While not all cases, particularly those with bilateral enlargement, are of primarily endocrine origin, a hormonal influence appears to be involved. As in many cases, the enlargement in this boy occurred during the adolescent period.

The case reported here resembles those described by Klinefelter, Reinfenstein, and Albright in many respects, but shows evidence of some decrease in androgenic function as well as the picture of low spermatogenic function seen in their cases. The local genitals were well developed and pubic hair was normal, but the development of a

beard was delayed, the testes were small, and prostate and seminal vesicles were not well developed. This was associated with a low excretion of 17-ketosteroids. It would appear that in this case there was some deficiency in androgens.

A.



B.

Fig. 3.—Appearance of breast tissue removed at operation. *A*, Gross appearance of masses removed from both breasts. *B*, Typical section through breast tissue.

Unlike the results reported by the Boston workers, we did obtain some reduction in mammary size during treatment with testosterone. This may have been due to more intense treatment on our part; again it may have been due to our ability to identify partial changes by the methods used. It is improbable that the change was coincidental since duplicate casts some time apart during the preliminary control period did not show such variation.

This change was apparently due to a direct effect on the gland, since there was no general loss of water or protein from the body; instead, the total weight increased. Since the glands were largely composed of connective tissue with occasional ducts and alveoli, it is probable that the shrinkage was in the ducts, and that there was a lower limit below which testosterone would have had no further effect. Perhaps if androgen therapy had continued for a sufficient time and had been checked by volume measurements, a similar decrease would have been found in the cases of Klinefelter and his associates. While surgical removal still remains the treatment of choice, the endocrine involvement in this syndrome should not be forgotten.

SUMMARY

1. A case of bilateral gynecomastia developing at puberty is reported in a 16-year-old boy. It was associated with little beard development and some evidence of improper or subnormal testicular function. The 17-ketosteroid output was low.

2. Administration of testosterone daily for three weeks decreased the volume of the breasts by about 50 per cent, while the general body weight increased. The excretion of 17-ketosteroids was also increased. The change in the gland appeared to be decreasing with time, however, and surgical removal was resorted to.

3. The histologic picture was one of chronic fibrous mastitis. The case appears to have been another of the syndrome described by Klinefelter, Reifenstein, and Albright.[5]

4. While a considerable reduction in the size of the breasts can be produced in these cases by intensive treatment with testosterone, the result is not sufficiently cosmetic, probably because of the increased residual connective tissue, to justify its use. The surgical approach is to be preferred. Androgen therapy can be used subsequently if it seems indicated.

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EFFECTS OF ENVIRONMENTAL TEMPERATURE ON THE TRAUMATIC SHOCK PRODUCED BY ISCHEMIC COMPRESSION OF THE EXTREMITIES

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CRUSHING injuries of the extremities may lead either to shock or to a delayed disturbance of renal function known as the crush syndrome. In a study[1] of an ischemic form of crushing injury in dogs, ten out of eleven of our experimental animals, studied at ordinary laboratory temperatures, died within a few hours after release of the compression with a shocklike course characterized by an initial rapid decline of mean arterial pressure followed by a slower progressive fall of pressure ending in death. Since the one survival occurred on a day when the temperature in the laboratory was unusually low we entered upon an investigation of the effects of environmental temperature upon the shock produced by this type of trauma, the results of which are presented in this paper.

METHODS

In this study both hind legs of dogs were crushed and rendered ischemic by applying a tightly wound spiral of rubber tubing from the ankle to the groin. The dogs were placed in cages and the rubber tubes removed after six hours. Administration of morphine, 4 mg. per kilogram, plus sodium pentobarbital, 20 mg. per kilogram, prevented pain during the period of compression but allowed the animals to be well awaked within one or two hours after release of the tubes. A few dogs received small additional injections of morphine during the period of compression.

A first group of sixteen control dogs was studied at ordinary laboratory temperatures which varied from 19.8° to 27.0° C. during the winter months and from 24.0° to 27.9° during May. A second group of fourteen dogs was kept in a cool environment in a room, maintained at 9° to 14° C., from the start of compression until twenty to twenty-four hours after removal of the rubber tubes. The dogs were then returned to the laboratory. Feeding was omitted on the morning of the experiment and water, available until the dogs were anesthetized, was withheld for the next thirty hours. Hematocrit readings were made of venipuncture blood. Rectal, intramuscular, and subcutaneous temperatures were recorded continuously.[2]

Read at the meeting of the American Medical Association, June 14, 1944, Section on Pathology and Physiology.

Supported by a grant from The Commonwealth Fund.

Received for publication, Sept. 7, 1944.

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The amount of edema in each traumatized leg was computed from the difference in the volume of water displaced when the leg was immersed in a tall narrow-mouthed cylindrical vessel before compression and again after death, or, in those dogs that survived, twenty-four hours after release of compression.

RESULTS

The dogs in both groups of experiments were, at the moment of release of compression, in varying stages of anesthesia from moderately deep to very light and a few in each group were attempting to sit up. Within a few minutes after release of the rubber tubes all the dogs became stuporous. Those kept in the laboratory usually remained semicomatose until death. In marked contrast to these, the dogs in a cool environment were found sitting up or standing within two to three hours after release of the compression.

The durations of survival of all dogs studied in this investigation are presented in Table I. This table clearly demonstrates that a cool environment during the period of compression and for a reasonable length of time afterward increases the viability of dogs subjected to this form of trauma.

The temperatures of the subcutaneous tissues and of the muscle of the compressed extremities declined rapidly after application of the rubber tubes and were approximately at the environmental temperature when the rubber tubes were removed. As a result, the temperature of the compressed tissues was considerably lower throughout the period of compression in the dogs kept in the refrigerated room than in those kept in the laboratory. The rectal temperatures of the control dogs were strikingly different from those kept in a cool environment. The former were between 35.3° and 41° C. until release of compression and then steadily rose, reaching temperatures of 39.0° to 43.1° C. at the time of death. The rectal temperatures of the latter ranged from 32.5° to 40° C. during compression, and in the case of all but one of the dogs that survived, remained relatively stable between 35° and 38.9° C. The rectal temperatures of five of the dogs in the refrigerated room dropped relatively rapidly to 28° to 34° C. during the night. These dogs were then warmed, but only one survived. The courses of the rectal temperature of a representative group of dogs are plotted in Fig. 1.

The dogs studied in May were weighed at the start of the experiment and again after death, or, if they survived, at twenty-four hours after release of the compression. Table I shows that the dogs kept in a cool environment and those in the laboratory lost approximately the same amount of weight, expressed in grams per kilogram of body weight. It should be noted, however, that the rate of loss of body weight was considerably more rapid in the latter group since their survival was much shorter than the thirty-hour interval between the initial and final weighing of the former group.

TABLE I

	NUMBER OF DOGS	DIED IN – HOURS AFTER RELEASE OF LIMB COMPRESSION			ENVIRONMENTAL TEMPERATURE ° C.		RECTAL TEMPERATURE ° C. DURING PERIOD OF LIMB COMPRESSION		AT RELEASE OF LIMB COMPRESSION		SIX HOURS AFTER RELEASE OF COMPRESSION OR AT DEATH IF SURVIVED LESS THAN 6 HOURS		24 HOURS AFTER RELEASE OF COMPRESSION OR AT DEATH IF SURVIVED 6 TO 24 HOURS	
		RANGE	AV.	σ	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.	RANGE	AV.
A1	1	Survived			19.8	19.8	35.6-39	37.3	38.0	38.0	39.2	39.2	37.0	37.0
A2	10	0.8-18	5.2	7.3	23-27	24.6	36.8-41.0	39.5	39.2-41.0	40.0	38.0-43.1	41.2	39.0	39.0*
B1	3	Survived			9-12	10.5	35.0-38.5	36.2	37.5-38.5	38.0	35.0-38.4	36.2	35.0-37.1	36.3
B2	4	22-48	35	14.2	9-12	10.5	35.5-40.0	37.3	35.5-40.0	37.1	29.0-33.9	31.3	26.5-36.0	29.6
C1	0	Survived			–	–	–	–	–	–	–	–	–	–
C2	5	4-19	8.2	5.9	24.0-27.9	26.5	35.3-40.3	38.1	37.0-40.0	38.7	39.2-41.5	40.0	41.2-42.0	41.1†
D1	6	Survived			10.3-13.0	12.3	32.5-38.0	35.8	33.0-39.0	36.9	35.0-38.9	36.9	36.5-39.0	37.9
D2	1	9.5	9.5	–	11.3	11.3	36.0-38.0	37.0	37.5	37.5	34.0	34.0	26.0	26.0

	WEIGHT LOSS IN GM. PER KG.		LOCAL EDEMA IN COMPRESSED LEGS						AUTOPSY OF LEGS, NUMBER OF DOGS IN EACH CATEGORY					STUDIED IN
			MEASURED		ESTIMATED MAXIMUM									
	RANGE	AV.	RANGE	AV.	RANGE	AV.	σ	AV. ERROR	0	+	++	+++	++++	
A1	–	–	–	–	–	–	–	–	–	–	–	–	–	
A2	–	–	3-35	17‡	15-49	30‡	13.7	8.5	2	5	2	1	0	Dec. to Feb. (controls)
B1	–	–	–	–	–	–	–	–	–	–	–	–	–	
B2	–	–	16	16§	29	29§	–	7.8	2	2	0	0	0	Dec. to Feb. (cool environment)
C1	–	–	–	–	–	–	–	–	–	–	–	–	–	
C2	29.5-59.0	39.9	26-41	34	39-56	48	5.9	5.8	0	0	2	0	3	May (controls)
D1	26.5-47.6	33.7	22-46	36	24-50	39	8.6	2.2	–	–	–	–	–	
D2	31.5	31.5	25	25	39	39	–	6.5	0	0	1	0	0	May (cool environment)

*One dog survived longer than six hours.
†Two dogs survived longer than six hours.
‡Edema measured on four dogs of this group.
§Edema measured on one dog of this group.

Survival, environmental, and rectal temperatures, weight loss, and local edema in anesthetized dogs traumatized by six hours of ischemic compression of their hind legs.

Av. = average. σ = standard deviation of individual determinations about the average, computed as:

$$\sigma = \sqrt{\frac{\Sigma(X-\bar{X})^2}{N-1}}$$, where X = individual determination on each dog, $\bar{X}$ = average of these determinations, and N = number of dogs.

The measured local edema in the compressed legs is expressed in ml. per kgm. of body weight. It is the sum of the edema in the two traumatized legs. In determining the volume of edema each hind leg was immersed three or more times during the control period before compression of the legs, and again after death, or in the case of a few of the dogs that survived, twenty-four hours after release of compression. The difference between the means of the control and post-mortem immersions divided by the weight of the dog gave the measured edema of the leg. Control experiments[1] indicated that an edematous leg shrinks approximately 5 ml. per kilogram of body weight when the animal dies. These studies also showed that approximately 10 per cent should be added to allow for edema of proximal tissues, not detected by the immersion method. Addition of these two corrections to the measured edema yields the volume which is tabulated as the estimated maximum edema.

Av. Error. This is an expression for the probable error of the estimated maximum edema. It was computed as follows: For each measurement of limb volume several immersions were made. The standard deviation of the difference between the control and the post-mortem volume for an extremity was computed as

$$\sigma I = \sqrt{\frac{\Sigma(\bar{X}_c - X_c)^2 + (X_{pm} - X_{pm})^2}{N_c - 1 + N_{pm} - 1}}$$

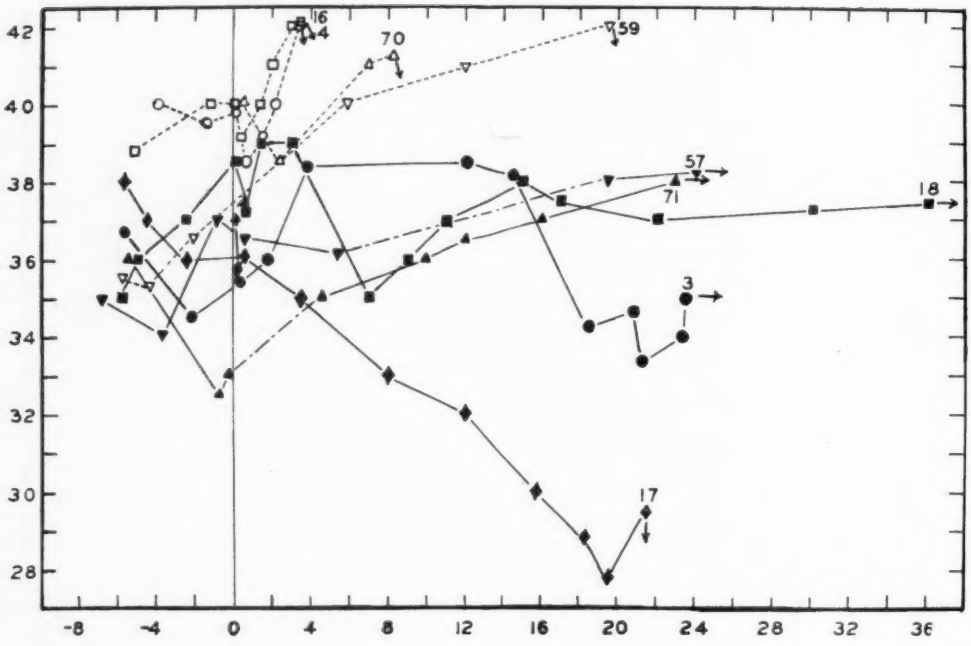
where X_c are the individual measurements at each immersion, $\bar{X}_c$ is the mean of these measurements during the control period, X_{pm} and X_{pm} are the corresponding measurements after death, and N_c and N_{pm} are the number of immersions, respectively. Using σ_s, the standard deviation for the change in volume of a leg with death,[1] = 2.0, then the total standard deviation for the estimated maximum edema in both legs in a dog is:

$$\Sigma\sigma = 2\sigma_s + \sigma I(R) + \sigma I(L)$$

In the table the column labeled Av. Error is the average of the $\Sigma\sigma$ for all the dogs in the group.

In the columns labeled Autopsy of Legs, + = just detectable moistness, ++ = obvious edema, +++ = marked gelatinous edema of the soft tissues, ++++ = marked gelatinous edema of the soft tissues with marked swelling and paleness of the compressed muscle.

Fig. 1.



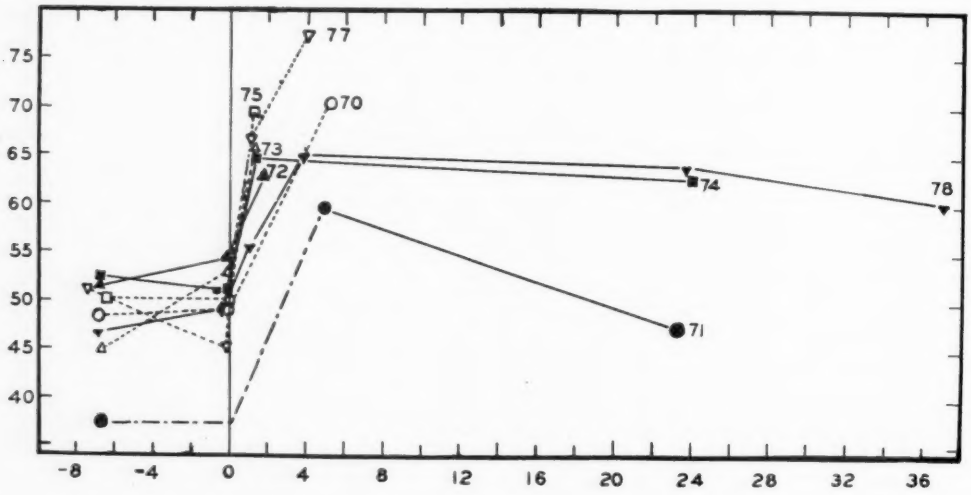


Fig. 2.

Fig. 1.—Plots of the rectal temperatures during and after application of ischemic compression to the hind legs of dogs anesthetized with morphine and sodium pentobarbital. Ordinate scale shows rectal temperature in degrees centigrade. Abscissal scale gives time in hours: zero time is moment of release of compression of hind extremities. Solid symbols and solid or dot-dash lines represent dogs kept in a cool environment, hollow symbols and dotted lines, dogs kept in the laboratory at ordinary temperatures. Corresponding symbols (for example, solid and hollow triangles) refer to animals studied simultaneously. Arrows with downward tip indicate the moment of death, arrows with tip pointing to right indicate complete survival. Dot—dash line signifies that temperature was not recorded continuously during the indicated interval.

Fig. 2.—Plots of the successive changes in hematocrit readings during and after trauma, as indicated in Fig. 1. Ordinate scale shows cell volume per cent of blood volume. Abscissal scale, symbols, and numbers have the same significance as in Fig. 1.

The hematocrit readings of the dogs kept in the laboratory rose somewhat more rapidly and reached higher levels than those of the dogs kept in a cool environment. These differences are illustrated in Fig. 2.

Post-mortem examinations were performed on all dogs that died. The findings in the traumatized legs are summarized in Table I. In addition to the varying degrees of edema, small hemorrhages were occasionally seen in the muscle or soft tissue. The traumatized muscles, particularly of the dogs studied in May, showed many regions of pallor. It has not been determined whether the pallor is due to loss of myoglobin or to separation of the muscle fibers by edema. Myoglobin has, however, been demonstrated in the urine of three dogs of another series of experiments which showed similar changes in the muscle. Occasional mild hyperemia of the lungs, omentum, and subcutaneous tissue of the thorax was seen in the dogs dying in the winter months, but no significant differences were noted between those dying at ordinary laboratory temperatures and those dying at low environmental temperatures. In contrast to these, all six of the dogs that died during May showed marked hyperemia of the cortex and papillae of the kidneys, and moderate to marked hyperemia of the subcutaneous tissue of the thorax, omentum, and duodenal mucosa. Free blood was found in the lumen of the duodenum of only one of the dogs kept in the laboratory and in the one which died in a cool environment.

Of the six dogs which survived in May, five were killed, two, five, nine, eleven and thirteen days after release of compression. Except for small superficial cutaneous ulcers on the traumatized legs of the last three dogs, all of the dogs were in good condition. Four of the five had lost 25 to 134 grams per kilogram of body weight, the larger losses occurring in the latter dogs. Essentially no residual edema was found on the eleventh or thirteenth days of survival, although small areas of pallor were observed in the crushed muscles. In the dogs killed on the second and fifth days the edema was as great as when measured twenty-four hours after release of compression. Except for moderate hyperemia of the duodenal mucosa, all other tissues were normal to gross examination.

Complete microscopic examinations* were made on two of the dogs which survived and were killed two and five days after release of the compression. In both dogs mild passive hyperemia and slight fatty metamorphosis were seen in the central zones of the liver. The epithelium of the tubules of the kidneys was narrowed and coarsely granular, and the proximal and distal tubules and the broad loop of Henle showed irregularly distributed foci of fatty degeneration. There was much acidophilic precipitate in the tubular lumen of the dog sacrificed after two days. The lumen of the glands of the duodenal mucosa contained what was apparently inspissated, deteriorated blood. In one dog the spleen showed diffuse slight fibrosis and the deposite of a great deal

*These studies were made by Dr. Howard T. Karsner, professor of Pathology and director of the Institute of Pathology.

of pigment of dark golden yellow and of light orange-yellow shades. The compressed muscle of the thighs showed various degrees of necrosis and hyaline degeneration. The cytoplasm was scanty and the nuclei of the muscle fibers were large and vesicular, each containing a nucleolus. Granulation tissue was present in the degenerating muscle and there was proliferation of large mononuclear cells, evidently of the sarcolemma. Fat stains were negative.

Table I shows that no significant difference was found between the *measured edema* of the dogs kept in the laboratory and those kept in a cool environment. When allowance is made, however, for certain technical errors of the immersion method,[1] the resulting volume, recorded as the *estimated maximum edema* in Table I, is found to be slightly greater in the former than in the latter.

Eight additional dogs were subjected to certain modifications of these experimental procedures during the winter months. The traumatized legs of two dogs were cooled by placing ice about them during the period of compression, while their bodies remained at room temperatures of 26° to 28° C. Both died in five and one-half hours. The traumatized legs of three dogs were placed in a chamber in which air, cooled to 7° to 14° C., was circulated while their bodies remained at room temperatures of 22° to 26° C. Two survived and one died at six hours. Concurrently with the latter dogs, the bodies of three dogs were placed in the cooling chamber while their legs remained at room temperature. One survived, the others died at six and eight and one-half hours.

During May, two dogs were kept at laboratory temperatures of 25.5° to 28.2° C. during the period of compression. Immediately after release of compression the dogs were placed in cages at environmental temperatures of 12° to 14° C. One was returned to the laboratory at twenty-four hours and died nine hours later; the other remained in the cool environment until it died at thirty hours.

DISCUSSION

The effects of warming or cooling traumatized extremities have been studied by Allen,[3, 4] Duncan and Blalock,[5] and Blalock.[6] These authors are all in agreement that cooling the traumatized extremities especially during the period of trauma lessens the severity of the shock and prolongs the survival. Blalock and Mason,[7] and more recently Antos[8] have studied the effects of a cool environment on the shock which follows a period of hypotension produced by bleeding. Both obtained a longer survival but no decrease in the per cent of fatality. Elman, Cox, Lischer, and Mueller[9] concluded that rats with severe body burns survived best at environmental temperatures near ordinary room temperature, and Wakim and Gatch[10] arrived at similar conclusions for rats, guinea pigs, and dogs traumatized by intestinal stripping. Unfortunately, little data is available regarding the rectal temperatures of the latter two groups of animals subjected to different environmental temperatures after trauma. Since the environmental temperature in their

experiments was the temperature of a platform on which the animals were placed, it is probable that the body temperatures were depressed below normal at environmental temperatures below normal body temperatures.

Our experiments demonstrate that controlled cooling of the body and legs during and after release of compression is an effective procedure in preventing this form of shock. Furthermore, there seems to be good evidence that whether the traumatized legs are cooled or not, placing the body in a cool environment increases the viability of anesthetized dogs subjected to ischemic compression trauma.

Four mechanisms require consideration in explaining the improved viability of our dogs exposed to a cool environment.

1. The lower temperature of the compressed tissues may have slowed metabolic action and tissue disintegration and, as a result, less toxic material may have entered the blood stream upon restoration of the circulation. Proof of this hypothesis must await evidence that blood returning from these traumatized extremities has a toxic action upon the body.

2. In addition to this, cooling might have reduced the vascular damage and thereby decreased the loss of plasma into the traumatized tissues. The somewhat smaller estimated maximum edema of the dogs in a cool environment and the slightly greater viability of the dogs whose extremities alone were cooled offer support for this hypothesis. However, the equally good results in those experiments in which the body only was cooled, or in which the dogs were placed in a cool environment only after release of compression, demonstrate that this mechanism is not the sole factor in explaining the better survival of our dogs placed in a cool environment.

3. It is commonly considered that a cool environment may aid by reinforcing compensatory cutaneous vasoconstriction. Since we wished to use minimal anesthesia and to allow our animals complete freedom of movement, it was not possible to study this factor in the present experiments.

4. As indicated by our records of mean arterial pressure, there occurs a marked depression of the circulation immediately after release of compression. Accompanying this, there is in all probability a diminution in the blood supply to vital tissues. In the presence of an elevated or even normal body temperature there is undoubtedly a discrepancy between the blood supply and the metabolic needs of these tissues during this period of circulatory depression. According to the proponents of the vicious cycle theory, this will lead in turn to further depression of the circulation and ultimately to death. On the other hand, the depressed circulation may be able to meet the demands of the tissues when their metabolism is reduced by lowering the body temperature and a fatal outcome may thereby be delayed or even obviated. This hypothesis is strongly supported by the observation that without exception in our experiments those dogs which survived maintained rectal temperatures

at or below 39° C. during the critical twenty-four hours after release of compression, whereas, all the dogs which died while kept at ordinary laboratory temperatures had rectal temperatures above this level during all or most of the time from release of compression to death. According to the observations of one of us (H. D. G.) and co-workers,[2] the normal range of rectal temperatures for dogs is 37° to 39° C. with an average of 38.5° C.

SUMMARY

Fifteen of sixteen anesthetized dogs subjected to a six-hour period of ischemic compression of their hind legs and kept at ordinary laboratory temperatures of 20° to 28° C. died in an average of 6.4 hours after release of the compression. Fourteen dogs were similarly traumatized but placed in a cool environment of 9° to 14° C. during and for twenty-four hours after the compression. With one exception all lived longer than twenty hours and nine survived indefinitely after release of compression. It is concluded that in these experiments the beneficial effect of the cool environment is due in part to diminishing the damage to the traumatized tissues during the period of compression, and in part to decreasing the metabolic demands upon the circulation by moderate lowering of the body temperature during the critical first twenty-four hours after release of compression. The evidence suggests, however, that rectal temperatures below 34° C. are not well tolerated. Facilitation of cutaneous vasoconstriction may also play a part, but evidence for this mechanism has not been obtained. Dogs studied in the spring reacted to this form of trauma with the production of more edema at the site of the compression and with more systemic hyperemia than did dogs studied in the winter.

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ARTERIAL SPASM SECONDARY TO LIGATION AND RETROGRADE INJECTION OF THE SAPHENOUS VEIN

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LIGATION of the internal saphenous vein at present is an accepted and commonly practiced procedure. The essential prerequisite for its execution has been the satisfactory demonstration of an adequate deep venous circulation by means of the various functional tests, the chief of which are those introduced by Trendelenburg, Perthes, Ochsner, and Mahorner. Accurate preliminary determination of the degree of arterial sufficiency to the part, however, has been commonly neglected. The experiences sustained in Cases 1 and 2 have suggested the study described in this report.

CASE REPORTS

CASE 1.—M. P., a white man, aged 54 years, came to us with varicose veins of the right leg and thigh. The symptoms were those of fatigue and discomfort along the inner aspect of the thigh after prolonged standing. There were no complaints suggestive of an impaired arterial circulation, such as intermittent claudication, coldness of the feet, disturbance of sensation, or fatigue on walking. The remainder of the present and past history was negative except for excessive smoking for many years, and a worrisome temperament.

Physical examination revealed a well-preserved and a fairly well-developed patient. The blood pressure was 145/90 and a routine urine analysis was negative. There were no remarkable physical findings except for the varicosities of the right lower extremity. The right leg and thigh presented a moderate-sized dilatation of the internal saphenous vein with tortuous branching dilatations over the inner upper two-thirds of the leg. Incompetency of the valves of the saphenous vein were readily demonstrated by means of the Trendelenburg test. Adequacy of the deep venous circulation was satisfactorily proved by both the Perthes, and the Ochsner and Mahorner tests. The arterial circulation in the foot seemed adequate, the dorsalis pedis and the posterior tibial pulses being readily palpable and of fair volume. The color and the temperature of the foot were normal and the Silbert passive flexion test failed to produce any abnormal degree of plantar ischemia. No oscillometric determinations had been made, this not having been part of the routine preoperative examination of that time.

Oct. 14, 1941, under local anesthesia, division and ligation of the right saphenous vein at the saphenofemoral junction were performed. Five cubic centimeters of 2 per cent sodium ricinoleate were injected into the distal segment at the time of operation. The immediate postoperative reaction and the convalescence were uneventful. In the following weeks sclerosing injections of 5 per cent sodium morrhuate were given to occlude the residual patent veins.

Oct. 28, 1941, following the injection of 1 c.c. of 5 per cent sodium morrhuate, the patient went into a state of profound allergic shock characterized by vomiting, cyanosis, absent blood pressure, extremely faint pulse, blood tinged expectoration, and diffuse urticaria. With appropriate treatment he recovered after one and one-half hours.

Received for publication, Oct. 6, 1944.

Nov. 21, 1941, the patient returned with the complaint of intermittent claudication occurring after walking a short distance. Examination at this time disclosed an absence of a palpable pulsation in the dorsalis pedis, posterior tibial, and popliteal arteries of the right leg. The right femoral pulsation in Scarpa's triangle could be obtained. The corresponding pulsations of the left leg were readily elicited.

Arterial occlusion of the vessels of the right lower extremity had evidently occurred. It was difficult to decide whether such a complication was the result of the ligation and retrograde injection of a sclerosing agent, or whether it was precipitated by the acute allergic shock that occurred at the later date.

CASE 2.—S. G., a white woman, aged 44 years, on examination was found to show moderately extensive varicosities of both legs with incompetent internal saphenous veins on both sides. The only complaints were the unsightliness and a sense of heaviness in both legs. Her health was good in all other respects and the antecedent history was irrelevant. Physical examination was negative except for the varicose veins as just described. The urine was negative. The feet were of normal color and exhibited good surface temperatures. Both dorsalis pedis and posterior tibial pulses were readily palpable and of good volume. Oscillometric determination taken at the lower third of the leg was 2 for each side. A bilateral saphenous ligation with retrograde injection of 5 c.c. of 2 per cent sodium ricinoleate on each side was done under local anesthesia in the customary fashion. The patient was made immediately ambulatory. Three days later she presented herself complaining of coldness of both feet. Examination disclosed a faint weak dorsalis pedis pulse on both sides with pallor and coldness of both feet. Oscillometric readings at the same level showed an excursion of ½. These findings persisted for two months, when the patient was lost trace of.

Accumulating clinical and experimental evidence shows that occlusion, chemical irritation, or bacterial inflammation of a segment of a large vein will cause ipsolateral reflex arterial spasm with diminution in the peripheral pulse volume. DeBakey, Burch, and Ochsner have shown that ligation of the proximal portion of the femoral vein in dogs resulted in marked diminution (52.5%) in the volume of the pulsations in the foot, as determined with the aid of an accurately recording plethysmograph. Preliminary resection of the corresponding paravertebral sympathetic ganglia or injection of novocain into the perivascular tissues of the isolated venous segment failed to influence the resultant decrease in volume of the arterial pulsations. This fall in pulse volume appears to have been due to the resultant increase of venous back pressure which was transmitted through the capillary bed against the arterial pressure. Subsequent injection of the chemical irritant into the lumen of this vein or into its perivascular tissues also produced a further marked decrease (51.6%) in the volume of the peripheral pulsations. In the latter case however, either preliminary resection of the paravertebral sympathetic ganglia or perivenous novocain infiltration into the segment of vein neutralized this action.

Reflex arterial spasm, secondary to severe thrombophlebitis, has become an accepted clinical entity. In extreme instances the ischemia resulting from such arterial spasm may simulate an arterial embolus or, where the spasm persists, may precipitate actual gangrene. Isolated

case reports of such occurrences have appeared increasingly in the literature in the past ten years. The syndrome evidently had been misinterpreted up to that time. The mechanism producing the arterial constriction is a sympathetic reflex caused by impulses originating in the involved venous segment. Paravertebral infiltration of the corresponding sympathetic ganglia with procaine will interrupt such reflex action. Similarly, perivenous infiltration of the venous segment with procaine prior to the injection of the chemical irritant also prevents the reflex spasm. The spasm resulting from the localized process in the vein, whether traumatic, bacterial, or chemical may occur in both arteries and veins. Injection of a potent sclerosing solution into a varicose vein results in a dramatically visible and palpable venospasm within one or two minutes. It is not uncommon for a dilated internal saphenous trunk one inch in diameter to shrink to the size of a lead pencil following the injection of 2 to 5 c.c. of a potent sclerosing agent. Traumatic venospasm is at times observed where repeated unsuccessful attempts at vein puncture have been made. This contractile power appears to be retained by dilated varicose veins, despite their atony, dilatation, and loss of elasticity.

Prompted by the experience in the two cases quoted, the following studies were entered into for the purpose of determining the effect that the clinical ligation of the saphenous vein together with the retrograde injection of a sclerosing agent had upon the arterial circulation.

PROCEDURE

The data were obtained from fifty consecutive cases in which saphenous vein ligations and retrograde injections were performed. The accepted prerequisites for saphenous vein ligation are:

1. A dilated internal saphenous trunk with incompetent valves
2. Patency of the deep veins as judged by the clinical appearance of the leg, together with the accepted functional tests.
3. General good health, as evidenced by the history, cardiac sufficiency, satisfactory blood pressure, and normal urine analysis
4. Adequate arterial circulation to the part, as determined by the history, the presence of palpable dorsalis pedis and posterior tibial pulsations, and a satisfactory appearance and surface temperature of the part
5. The absence of acute phlebitis, acute inflammation, or grossly infected ulceration
6. An oscillometric determination within normal limits

The patients were ambulatory prior to the operation, receiving a preliminary oral dose of 1½ gr. of sodium pentobarbital. The blood pressure (brachial) was taken preoperatively and postoperatively in twenty patients. Oscillometric determinations were made in the lower third of the leg at constricting pressures of 160, 140, and 120 mm. of mercury.

Simultaneous oscillometric readings were taken pre- and postoperatively in the forearm in ten patients and in the leg upon which operation was not done in ten other patients.

The skin and tissues over and about the saphenofemoral junction were infiltrated with 1 per cent novocain free of adrenalin. The proximal portion of the saphenous trunk was exposed by a two-inch horizontal incision made directly over the fossa ovalis. The segment of the vein was isolated from its sheath for a distance of three inches below the saphenofemoral junction. It was clamped, divided, and resected for a distance of two inches. The proximal and distal ends were transfixed and ligated. From 3 to 5 c.c. of 2 per cent sodium ricinoleate, in accordance with the size of the vein, were injected into the distal segment.

In ten patients oscillometric readings were taken immediately following division of the vein and again directly after injection. In all patients, oscillometric readings were taken at the completion of the operation or approximately within fifteen minutes after injection of the sclerosing solution. Readings were taken again one hour after the injection. Ten patients were hospitalized and readings made over a twenty-four hour period. All patients were made immediately ambulatory, so as to diminish the hazard of postoperative emboli. A Collin oscillometer was used for all determinations. The accepted normal oscillation was found to vary from two to six.

RESULTS

In evaluating the effects of surgical venous trauma and chemically produced phlebitis any appreciable deviation in the oscillometric reading from the preoperative normal was considered evidence of arterial spasm. No untoward reactions followed the procedure. There was no evidence of novocain shock or sensitivity to the sclerosing agent in any of the patients. In most instances there was a burning or cramplike sensation in the leg shortly after the retrograde injection of the sodium ricinoleate, which persisted for varying lengths of time. In many patients this would be followed by the subjective and objective signs of a chemical phlebitis in the veins of the thigh and leg, to a varying degree. The arterial spasm seemed to be roughly proportionate to the degree of immediate postoperative discomfort, that is, the more the burning and cramp, the greater the drop in the oscillometric reading. In most instances the maximum arterial spasm was detected about thirty minutes postoperatively.

1. There was no appreciable change in the postoperative brachial blood pressure as compared with the preoperative reading in any of the twenty patients so studied. This would tend to show that any resultant arterial spasm in the leg produced no recognizable effect upon the systemic blood pressure.

2. Oscillometric readings taken in the upper extremity directly following those taken in the involved legs showed no change from the preoperative determinations. Likewise, readings taken in the opposite

leg, when that extremity was not treated by ligation and retrograde injection, showed no change from the readings obtained preoperatively. This would tend to corroborate the clinical and experimental work of Leriche, Ochsner and DeBakey, and DeBakey, Burch, and Ochsner, in that the arterial spasm secondary to a phlebitic process is reflex and is confined solely to the homologous extremity.

3. In five patients no change in oscillometric readings occurred up to ninety minutes postoperative. In one instance the readings were higher by 1 to 2 points. No certain explanation can be given for these latter inconsistencies. The chemical phlebitis may not have been sufficiently severe to produce a reflex arterial spasm. The spasm might have been transitory, having possibly occurred in between the readings, which were taken every fifteen to thirty minutes.

4. In ten patients, readings were taken immediately after division and ligation of the vein, but before the sclerosing solution was injected into the distal segment. No change was noted in any of these. This would tend to show that trauma upon a small segment of the vein was not sufficient to produce a reflex arterial spasm of sufficient degree to be detected by our method of study. DeBakey, Burch, and Ochsner, however, were able to produce experimentally increased intra-arterial pressure, as determined by the plethysmograph, by exclusion without division of a small segment of the femoral vein.

5. In forty-five patients there were definite postoperative falls in the oscillometric readings. Since the preoperative oscillometric determinations varied from 2 to 6, it was thought best to interpret the degree of arterial spasm in terms of percentage deviation from normal rather than the actual change in scale reading of the oscillation itself. For example, a patient with a preoperative reading of 6 and a postoperative reading of 2 would have a percentage change in oscillometric reading of 66 per cent. This showed a mean change of 54 per cent, the individual minimum being 20 per cent and the individual maximum 75 per cent.

The arterial spasm appeared from five to thirty minutes after the retrograde injection, reached its peak from thirty to sixty minutes after such injection, and usually returned to normal in four to six hours. Ten of these forty-five patients were observed over a period of twenty-four hours. Eight of these exhibited normal readings at the end of this time, whereas two still showed a persistence of arterial spasm at the end of the twenty-four hours.

INTERPRETATION

In the use of the oscillometer the occurrence and degree of arterial spasm has been gauged by an indirect method rather than by direct determinations on the arteries themselves. The difficulties of direct measurements of intra-arterial pressures in human beings are obvious. Oscillometric determinations have been universally accepted as a satisfactory means of determining the adequacy of the circulation in the larger arteries, even though the patency of the small arteries and

arterioles cannot be detected in this way. It was felt that this method of detecting arterial spasm was adequate for these studies, and one that could roughly lend itself to quantitative clinical application.

This study has been a clinical evaluation of the effect upon the arterial circulation by the presently accepted combination procedure of saphenous ligation and retrograde injection of a sclerosing agent. Arterial spasm followed the division and retrograde sclerosis of the saphenous vein. It did not appear directly after the division and ligation of the vein. Since it did appear at varying intervals after the irritative effects of the sclerosing agent, and since it was roughly proportional to the degree of reaction, one is prone to attribute the resultant spasm to the induced chemical phlebitis. No attempt had been made to determine the occurrence of delayed arterial spasm in a series of cases where just division and ligation of the vein had been performed. It is noted by us, and by others, that ligation and division of the saphenous vein alone would be followed by collapse, occlusion, and thrombosis of the vein distal to the level of the ligation. Such effect might also induce a reflex arterial spasm and may be worthy of investigation.

CONCLUSIONS

1. The results of this study confirm experimental findings and clinical observations that phlebitis, either chemical, infectious, or traumatic, may produce reflex arterial spasm.

2. The widely practiced procedure of saphenous ligation and retrograde injection of a sclerosing agent is commonly followed by a varying degree of arterial spasm in the homologous extremity.

3. Such resultant arterial spasm may precipitate a further increase of arterial circulatory insufficiency in instances where an impaired arterial circulation already exists.

4. These observations emphasize the necessity for the determination of the degree of arterial sufficiency to the part when division and retrograde injection of the saphenous vein are anticipated. Precipitation of an impending or partial arterial occlusion into a more complete form may result from the arterial spasm induced by this procedure.

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VASCULAR INSUFFICIENCY OF THE LOWER EXTREMITY DUE TO OSTEOMA OF THE FEMUR

Case Report

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IN THIS paper is reported a patient with typical intermittent claudication relieved by removal of an osteoma of the femur.

Impairment of the blood supply of the lower extremity is a relatively common occurrence. In the great majority of cases the diminution in blood flow is due to intrinsic lesions in the walls of the arteries and veins. Nové-Josserand* has reported a case in which the femoral artery was traumatized against an underlying femoral exostosis, producing a false aneurysm which caused impairment of the arterial supply of the lower leg. Perusal of the literature has failed to reveal a case in which vascular obstruction was caused by a benign tumor of the femur.

CASE REPORT

A. G., a 48-year-old white man, was admitted to the Orthopedic Service of Barnes Hospital, July 18, 1944, and was discharged July 27, 1944. Sixteen years previous to admission the patient had noted a hard, painless swelling on the medial aspect of the left thigh just above the knee. This swelling gradually increased to the size of a hen's egg over a period of six years, following which it had ceased to enlarge. Except for the presence of the tumor itself, the lesion had been asymptomatic until four years prior to admission when the patient began to notice that the left leg tired more easily than the right. This gradually increased in severity until seven months previous to admission when he developed intermittent claudication of the left leg. He was unable to walk more than a city block without experiencing severe pain in the left calf. The pain necessitated his resting, which immediately brought relief. The pain was described as a severe ache—"My calf felt like it was going to burst out." The patient volunteered that the pain and walking were always accompanied by a great distention of the veins of the lower extremity. The pain so incapacitated the patient that he was forced to cease working two months previous to admission to the hospital. At that time he developed severe pain whenever he attempted to walk more than ten steps.

On admission to the hospital the physical and laboratory examinations were essentially normal, with the exception of those relating to the local lesion. There was a hard, fixed, nontender mass 5 by 6 cm. in diameter located on the medial supracondylar line 10 cm. from the distal end of the left femur. The left foot and lower extremity were cooler than the right, and the left dorsalis pedis and posterior tibial arteries could not be palpated. There were no tropic changes in the nails or skin. When the patient was in the supine position there was definite engorgement of the veins of the left lower leg. There were a few small varicosities around the malleoli. The skin in this region showed a dusky cyanotic discoloration. The cyanosis and the venous distention were increased in the dependent position. On elevation of the extremity the veins emptied slowly and the foot became slightly pallid. When the patient walked a few steps there was a great increase in the engorgement of the superficial veins and in the cyanosis of the lower leg. The tumor did not encroach up-

Received for Publication, Oct. 2, 1944.

*Nové-Josserand, M.: Déchirure de l'artére femorale pars une exostose ostéogénique, Lyon chir. 24: 234, 1927.

on the long saphenous vein. There was no edema. Radiographs showed a typical osteochondroma of the left femur with some calcification of the femoral artery proximal to the lesion.

Although it was thought that the osteoma and the vascular impairment probably were not related, it was decided that the tumor should be removed. At operation, on exposing the area it was found that the pedicle of the osteoma was located on the medial supracondylar line just distal to the tendinous ring through which pass the

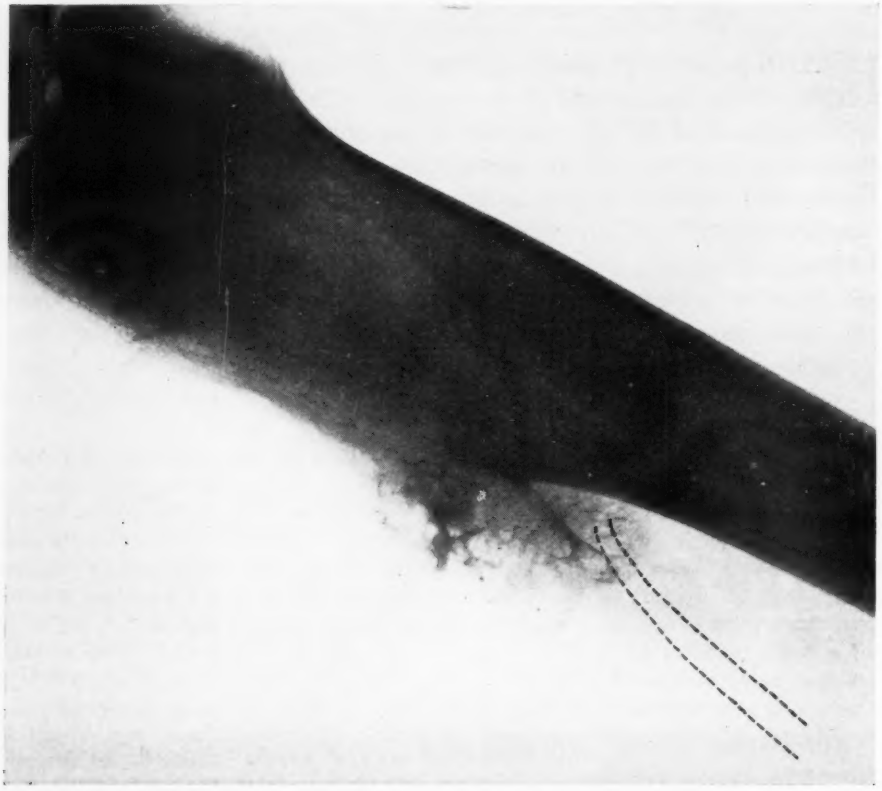

Fig. 1.—Osteoma of the femur which obstructed the femoral artery and vein by compressing them against the tendon of the adductor magnus. The femoral artery, showing calcification in the wall which was clearly visible in the original radiograph, has been delineated in this print.

femoral artery and vein. From its pedicle the tumor had grown superiorly in two walnut-sized masses, one anterior and one posterior to the tendon of the adductor magnus. The Y formed by these two masses compressed the great vessels against the rigid superior margin of the tendinous ring, causing considerable distortion of the vessels and diminution of their lumina. The pulsations of the femoral artery distal to the lesion were present, but markedly diminished in volume. The femoral vein was dilated distal to the obstruction so that the diameter of the distal segment was about twice that of the proximal segment. The osteoma was removed and the wound closed in the routine manner. Pathologic diagnosis of the removed tissue was osteoma of cortical bone.

The patient's postoperative course was uneventful. He was allowed out of bed on the fourth postoperative day and volunteered that for the first time in three years he was able to walk without pain. At the time of discharge no pulsations could be palpated in the left dorsalis pedis or posterior tibial arteries. The skin temperature was higher than it had been before operation, but it was still somewhat lower than that of the right foot. The venous engorgement had almost entirely disappeared. Two months following operation the patient still had some weakness of the left

leg and the extremity felt tired after prolonged exercise. However, he was back at work and there was no recurrence of the intermittent claudication.

COMMENT

This patient's circulatory disturbance apparently was due largely to the partial obstruction of the femoral artery and vein by the osteoma of the femur. The blood flow in the femoral artery was further decreased by the arteriosclerosis in the wall. This process in the vessel wall apparently was caused by the trauma, and constriction of the vessel by the tumor. There were no signs or symptoms of arteriosclerosis in the opposite lower extremity, nor could calcification be seen in the radiograph, or at operation, distal to the lesion. The onset of symptoms did not occur until thirteen years after the appearance of the tumor and seven years after the patient thought it had ceased to grow. This was due to two factors: (1) There was probably continued occult growth of the tumor into the soft tissues of the thigh after subjective enlargement had ceased; and (2) there must have been a gradual increase in the arteriosclerotic process in the arterial walls, both generally and locally, which did not reach a critical point until approximately four years prior to admission, when the patient first developed symptoms. This patient had a gradual occlusion of the femoral artery extending over a period of sixteen years, and yet adequate collateral circulation had failed to develop. This is consistent with the well-known paucity of anastomotic channels around the knee joint. The failure of edema to develop in the presence of markedly increased venous pressure demonstrates very nicely the fact that venous obstruction alone does not cause fluid retention in the tissues.

Although the impairment of venous return was the most striking feature, it seems unlikely that this could have been responsible for the intermittent claudication. The case throws an interesting light on the controversial principle of ligation of the main vein of an extremity when the main artery is occluded. In this case the obstruction of the femoral vein was of a higher degree than that of the femoral artery. Following operation there was clinically a great improvement in the venous return without noticeable change in the arterial inflow. The fact that the patient's circulatory efficiency was obviously greatly increased after the operation by the improvement of venous return is a point against the validity of these principles. Symptomatic relief following operation was dramatic despite the failure of the arterial pulsations in the foot to return to normal. The continued absence of the pulsations was no doubt due to the secondary arteriosclerotic process in the wall of the femoral artery at the site of the tumor.

SUMMARY

A case of intermittent claudication relieved by removal of an osteoma of the femur is presented. The vascular insufficiency was caused by obstruction of the femoral artery and vein by the tumor and by secondary arteriosclerosis of the artery.

PLASTIC CLOSURE OF SKULL DEFECT

Case Report Illustrating Use of Tantalum Plate and Pedicle-Tube Graft

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THE repair of skull defects caused by war injuries to military personnel has become a technical procedure of increasing importance in rehabilitation neurosurgery. Unpublished statistics collected from the existing neurosurgical centers in the Zone of the Interior show that a large proportion of such casualties may be returned to duty. Following the reports of Pudenz[1] and Pudenz and Odom,[2] tantalum plate has been used extensively for this purpose. Its strength, malleability, and lack of tissue reaction have recommended its clinical trial in an increasing number of cases. The various techniques for the formation and for the fixation of the plate have been described and found adequate in a sufficiently large number of cases.[3]

Cranioplasty in otherwise normal individuals, that is, individuals without grave neurologic defect and convulsions, may be complicated by residual infection in the scalp, dura, or brain. It may be further complicated by the necessity for staged procedures, and frequently by the problem of extensive scalp loss and its replacement by thin, atrophic scar tissue. Proposed incisions for cranioplasty for war wounds of the head must be placed with due attention to the vascular supply of the involved scalp tissue. The failure to appreciate fully this fundamental surgical principle in a formidable instance of scalp loss and the subsequent course of uncharted surgical therapy are illustrated in Case 1.

CASE REPORT

Case 1.—Aug. 7, 1943, a 30-year-old soldier received a severe penetrating wound of the left frontal region of the head when struck by a fragment of an 88 mm. shell. The missile produced a compound, comminuted, depressed fracture of the left frontal bone with dural and cerebral laceration. Incomplete débridement was performed forty-eight hours later. The wound became infected, and on Aug. 21, 1943, a secondary débridement was carried out with removal of bone fragments and two foreign bodies. A roentgenogram of the skull taken before this procedure shows the extent and character of the bony defect and the presence of a large shell fragment (Fig. 1). The resulting cerebral fungus subsided, and by September 22, healing was complete. During the first month following injury the patient was described as semistuporous, irrational, and irritable. There was cervical rigidity and weakness of the right upper extremity.

Upon admission to the Ashford General Hospital, Nov. 15, 1943, the neurologic examination showed normal findings. There was a pulsating, locally tender skull defect in the left frontal region, covered by a large, stellate, thin and atrophic scar (Fig. 2). The mobility of the scalp was limited. The extent of the scar, its

Received for publication, Nov. 16, 1944.

location outside the hairline, and the limited mobility of the scalp, appeared to prohibit a massive shift of scalp tissue rostrally, with its attendant secondary scalp defect. A primary pedicle graft was not considered. A decision was reached to carry out a concealed left frontal craniotomy incision well caudal to the scar, to dissect the scalp scar from the underlying cerebral cicatrix, to replace the dura by appropriate means, and to insert the tantalum plate with the hope that the atrophic scalp scar would remain viable. After healing of the proposed dural and skull graft, a secondary plastic revision of the scalp was considered a less dangerous procedure.

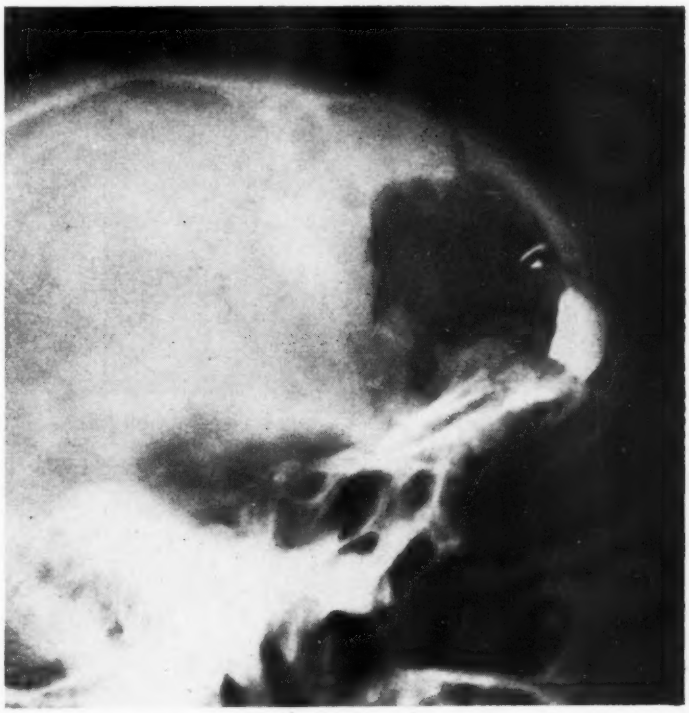

Fig. 1.—X-ray of the skull, showing defect and presence of shell fragment.

Dec. 15, 1943, the scalp flap was reflected. A partially reformed dura was grafted and closed with interrupted sutures of fine silk. A slight leak of subarachnoid fluid persisted between these sutures at the termination of this phase of the repair. A well-fitting, preformed tantalum plate was inserted, and fixation was secured by means of tantalum wire sutures. The scalp flap was closed by the customary two-layer method of suture. At this time the broad scar appeared somewhat cyanotic. (Repair by B. W.)

At the end of three days the greater part of the scalp scar had become gangrenous and had sloughed, exposing the underlying tantalum plate (Fig. 3). Culture of an associated purulent discharge showed a hemolytic *Staphylococcus aureus*. Pyogenic invasion of the central nervous system seemed inevitable. Penicillin therapy was started with 30,000 units given intravenously every two hours for eight days; 15,000 units every three hours for three days; and thereafter, because of local irritation, 25,000 units intravenously every three hours for 120 days. Packs saturated with penicillin, 100,000 units per cubic centimeter, were placed in the defect once daily. At no time was there any evidence of localized or generalized infection of the central nervous system.

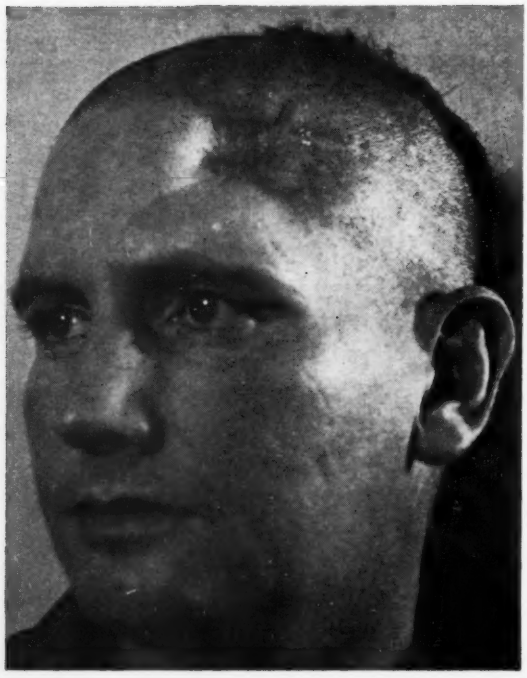

Fig. 2.—The patient before operation, showing thin adherent scar.

Fig. 3.—The patient after operation, showing the exposed tantalum plate after sloughing of the scar.

A.

B.

Fig. 4.—*A*, The appearance of the pedicle-tube graft raised from the left arm. *B*, Showing the first stage of transference of graft to scalp defect.

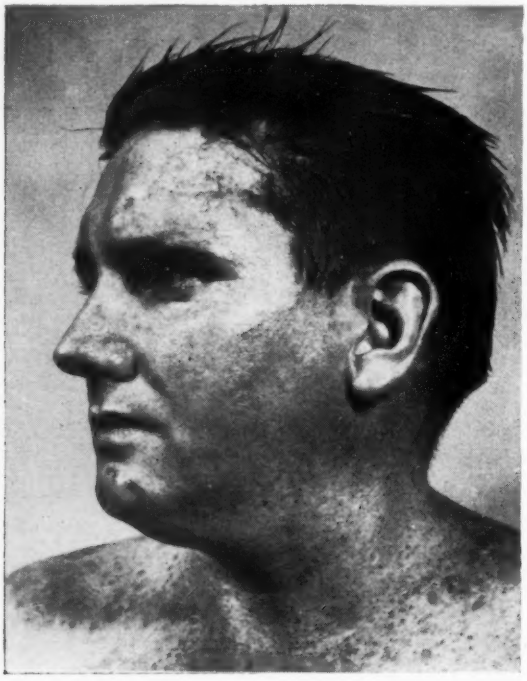

Fig. 5.—The appearance of the graft at the time of the patient's discharge.

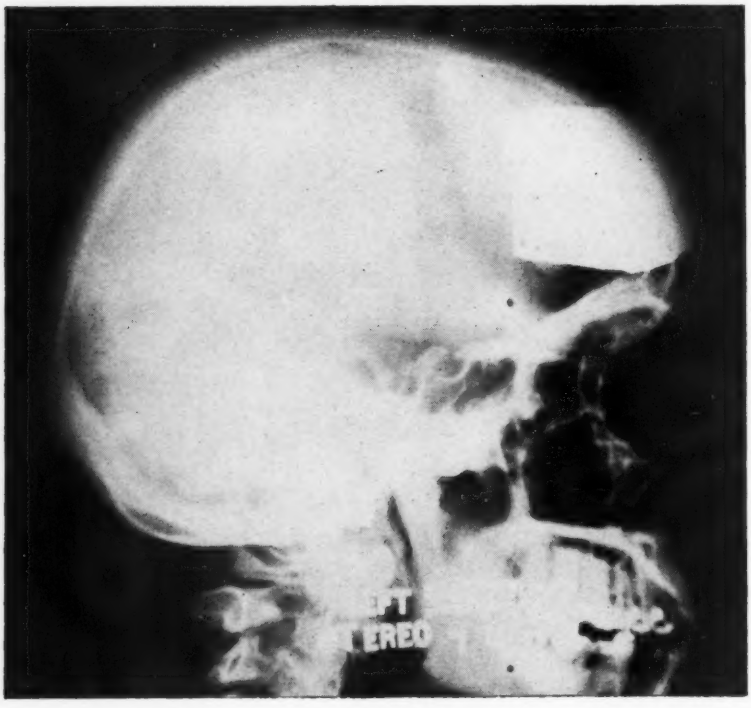

Fig. 6.—X-ray of the skull at the time of the patient's discharge, showing tantalum plate.

Jan. 3, 1944, a double pedicle graft was prepared on the anterolateral aspect of the left arm (Fig. 4*A*). On January 28, the proximal end of the graft was detached, sutured to the edges of the scalp defect, and held in place by a specially devised arm brace (Fig. 4*B*). On February 17, the remaining pedicle was resected. Complete closure of the scalp defect was carried out April 8, and thereafter the graft healed perfectly (This stage performed by M. H. H.). The appearance of the graft at the time of discharge, June 1, 1944, and the roentgenogram of the skull repair are illustrated (Figs. 5 and 6).

DISCUSSION

The plastic revision of scalp defects has been accomplished in the past by the usual methods of transference of skin from other areas of the body, by secondary relaxing incisions, by undercutting the margins of the scalp defect, by stretching of the scalp, by the use of pedicled flaps of adjacent scalp tissue, and by such elaborate multiple, pedicle graft revisions as described by Tillmanns (Fomon[4]). When the skull is denuded of pericranium, multiple diploic perforations may cause the development of a bed of granulation tissue upon which skin may be transplanted. The problem of replacing extensive scalp scars that are directly adherent to underlying cerebral cicatrices by normal scalp tissue has not received detailed attention. Cutaneous cerebral scars of sufficient magnitude to demand plastic repair may not be uncommon following massive, excavating war wounds of the brain, particularly as a sequel to the regression of a cerebral fungus. Although determined efforts are made by neurosurgeons in active theaters to carry out primary closure without tension with the aid of extensive plastic procedures, the onset of wound infection may vitiate these efforts in a low percentage of cases.[5-7]

The surgical principle involved in the repair of cutaneous cerebral scars appears to be the prevention of central nervous system infection, no matter what specific method of plastic revision is selected. This necessitates complete closure of the dura by suture or graft, and a closure immune to infection is not technically possible. It follows, therefore, that a potential infection must be prevented by bactericidal or bacteriostatic means. No method of plastic revision of a scar of this character will insure a primary closure of the operative field with the possible exception of a large pedicle graft from adjacent scalp tissue, with its deforming sequel.

The method described in this instance may be a partial solution to this problem. Although the penicillin therapy was undoubtedly overemphasized and unnecessarily prolonged in the light of more recent experience, it appears indisputable that a potential invasive infection may be prevented with penicillin therapy. The sequence of events in this patient has demonstrated the remarkable but characteristic inertness of the element tantalum in tissues. Successful pedicle grafting over a tantalum plate has not been recorded in surgical experience, but there appeared to be no delay in the customary healing time of such grafts. Moreover, the final cosmetic result was satisfactory.

CONCLUSION

Large cutaneous cerebral scars subsequent to extensive war wounds of the head present a problem in plastic revision that has not been solved. A case has been presented in which, through an error in operative technique, a tantalum plate was exposed after gangrene of an overlying, thin, atrophic scalp scar. Invasive infection of the brain was prevented by the use of penicillin while a pedicle graft was prepared and sutured into the resulting scalp defect. Healing of the pedicle graft sutured over the tantalum plate proceeded normally, and satisfactory cosmetic result was obtained. Such a procedure, or a composite variation with primary preparation of the pedicle graft, may offer a solution to this troublesome sequel of head injury.

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PSYCHOSOMATIC FACTORS IN SURGICAL PRACTICE

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THE inability to find an organic basis for a patient's symptoms often poses the most perplexing problem which a surgeon must face. The easiest solution places the patient in the position of being a malingerer, or a neurotic, or in some other category of functional disorders. Physicians who have little insight, or great disinterest, in psychosomatics are inclined to tell the patient reassuringly that there is nothing wrong, and to urge him to "forget it." But try as he may, the patient cannot forget the persisting vertigo, epigastric pain, bloating, and other symptoms, and he consults another doctor about the operation he is sure he needs.

In surgical practice it not infrequently happens that operations are performed for definite organic pathology, which are successful when measured by every accepted standard. Yet the patient complains of the recurrence of the same symptoms, or develops a new group which may not be at all closely related to the previous condition, and is bewildered and resentful when he is told that he is imagining things.

It is well known that emotional disturbances may express themselves through the viscera and other organs, working via the autonomic nervous system to produce symptoms which, as has been well said,[1] "are as little the result of voluntary processes or conscious intent as pulmonary tuberculosis, carcinoma, or heart disease, and equally amenable to the magic of kind words or admonitions." These disturbances may have their roots in such difficulties as marital maladjustment, financial reverses, frustrations and feelings of insecurity or inferiority. The symptoms so produced can be relieved only by treatment of the cause, that is, by straightening out the patient's psychic tangle.

This is not a new concept. The art and science of medical practice are as old as medicine itself. But in this day of precision and mathematical application, we are inclined to overemphasize the science and underestimate the art of practice.

The art of practice deals with the treatment of the patient as a whole, interacting with his particular environment. Extremely significant are the family and friends who comprise the social environment. A more talented sibling, a disgruntled spouse, or a demanding mother-in-law may spark the symptoms which are so distressing. A loafing business partner, an inadequately staffed office, a strike at the plant, or the marriage of an efficient secretary may start rolling a long train of trouble.

Received for publication, Nov. 13, 1944.

The recent medical literature is replete with evidence of the current interest in psychosomatic medicine. A quarterly periodical bearing the title *Psychosomatic Medicine* is a newcomer in the ranks of accepted medical journals. In 1943, a full-grown text, *Psychosomatic Medicine*,[2] the first of its kind, was published by two well-known teaching clinicians. This is a practical guide which should be of aid to every practitioner. It was followed by another volume, *Psychosomatic Diagnosis*,[3] an informative and revealing book. The last revision of Sir William Osler's *Principles and Practice of Medicine*[4] devoted the first forty-eight pages to psychosomatic interests. For years Alvarez has pleaded with the physician to study psychogenic symptoms instead of brusquely dismissing patients because of their "imaginary" complaints. In the preface to his new book,[5] an exceedingly valuable treatise, he said:

> This is a "different" sort of book—one which deals more with sick unhappy persons than with their diseases, more with symptoms and their meaning than with disease entities, more with the handling of patients than with the giving of medicines, and more with the puzzling, poorly understood and poorly described abdominal discomforts and indigestions than with the well-known organic diseases such as ulcer, cholecystitis and cancer.

Gastroenterology is, of course, the field in which psychosomatic symptoms are most obvious. Even a child learns that too much excitement, like too much candy, makes him sick at his stomach. Nevertheless, psychogenic factors do not, even now, always receive the attention they merit. A recent three-volume study of gastroenterology was criticized because in the consideration of symptomatology the space devoted to psychogenic factors was inadequate from the modern point of view, and not enough attention was paid the relationship of psychosomatic factors to ulcer of the stomach and duodenum.[6] This criticism, in contrast to the work criticized, indicates the growing recognition of the importance of psychosomatic medicine.

Smith and Rivers[7] noted the relative unimportance of the diet in the treatment of many ulcers, as shown by the fact that an ulcer may cause severe symptoms which remain unchanged in spite of treatment, until the clearing up of some nervous factor leads to prompt relief. These authors stated that the nervous factor is the dominant causative factor and added: "It is not necessary to psychoanalyze the patient to treat the nervous factors. It is necessary to teach the patient to know himself, his weaknesses and his nervous characteristics and to realize their effect on his ulcer."

Wakefield and Mayo,[8] in 1938, directed attention to functional disorders of the colon. They said:

> The clinical history of a functional disorder of the colon may subjectively reveal the presence of every known symptom which can arise from organic disease of the colon. . . . In eliciting the history, there are certain facts to be ascertained. Organic disease is likely to be ushered in with fever, loss of

weight and perhaps blood in the stool. A functional disorder arises during or following the stress and strain of a social crisis.

These authors described in detail the means of distinguishing between functional and organic disease of the colon, and declared that when careful and complete examination reveals no somatic disease, it is essential to explain to the patient that the symptoms are derived from the autonomic nervous system and are not organic. They concluded:

> Surgical treatment of the functional disorders of the colon, as an adjunct to rational therapy, is definitely contraindicated. When operation is performed in the absence of organic disease, it denotes an error in surgical judgment . . . . A patient with a functional disorder of the colon may require surgical intervention for other abdominal disease, and fine differential diagnostic judgment is often required in such cases. When it is necessary to operate under these circumstances, it is important to make sure that the patient understands that the proposed operation is not intended to alleviate those abdominal symptoms referable to the functional disease. Surgical advice, therefore, in functional diseases of the colon consists, for the most part, of advice against surgical intervention.

An operation will not cure all of a patient's symptoms unless these are all due to the lesion for which the operation is performed. Brooks[9] reported that of fourteen consecutive patients operated upon for acute appendicitis, all of whom were observed at operation to have definite acute inflammatory process in the appendix, seven were found on postoperative psychiatric examination to have evidences of anxiety sufficiently grave to be of clinical significance. Two patients operated upon during the same period, who showed no organic change in the appendix, disclosed sufficient evidence to warrant the conclusion that the symptoms and signs which led the surgeon to operate were in reality manifestations of neurosis.

Psychogenic factors in gynecology and obstetrics received extensive editorial comment in *The Journal of the American Medical Association* in 1937. The Journal cited Mayer and stated:[10]

> Pelvic symptoms are exaggerated more readily than others because many emotional conflicts of women resulting from personal and social restrictions, besides the normal processes of menstruation, defloration and childbirth (all associated with pain and bleeding), center attention on the genital zone and predispose to undue anxiety in connection with local symptoms. The functional cycles are under endocrine control, which is influenced by changes in the sympathetic nervous apparatus, increasing the vulnerability. Acute or chronic psychologic influences, such as fear or frustrated hopes, are associated not only with symptoms but with organic change. Amenorrhea may be a symptom of mental disorders of wide range. Irregular or excessive bleeding may have a psychopathic basis, although here diagnostic curettage should precede the drawing of such a conclusion. Prolonged mental treatment may be needed in dysmenorrhea, in which psychogenic factors are responsible or at least contributory. Certainly expert psychotherapy is indicated before radical operative intervention is attempted.

Seven years later a wartime communication from the Philippines provided striking evidence that amenorrhea may be of emotional origin. Whiteacre and Berrera,[11] having observed the women in the Santo Tomas internment camp in Manila, wrote that 14.8 per cent of them suffered from amenorrhea probably due to "severe psychic shock, worry and fear, which, acting through the autonomic nervous system, caused a complete suppression of ovarian function." Food deficiencies, chronic diseases, and other factors, these authors stated, were ruled out.

Psychosomatic symptoms may, of course, direct attention to other than gastric or gynecologic problems. Douglas-Wilson,[12] writing on the somatic manifestations of psychoneurosis, suggested the protean nature of psychogenic functional symptoms. He studied 231 psychoneurotic patients in a military hospital and said:

> Nearly all exhibited localized symptoms referred to various organic systems. Cardiovascular disorders such as dyspnea, palpitation and precordial oppression were frequently the most distressing complaints. In other instances the primary symptomatology was referred to the chest, the central nervous system or the digestive and urinary tracts or was constituted by general manifestations, including weakness, nervousness, headache and dizziness.

When after painstaking examination the surgeon discovers that his symptom-ridden patient is free from organic disease, what is he to do? He may by this time have an inkling of the source of emotional conflict or fear. Is it proper for him to try to handle the situation himself? The Journal editorial previously quoted concludes:

> Some objections have been raised as to the propriety of the administration of psychotherapy by one who is treating organic ills as well, but in the great majority of cases no ground for such objection exists. Most of these patients do not require formal psychoanalysis but perhaps only simple suggestive treatment, which is best received by their own physician. What is obviously required is the gaining of the patient's complete confidence, an intelligent psychanamnesis, the removal of anxiety where possible, assistance in the acceptance of a reality, instead of a retreat from it, perhaps a change of environment, a building up of the general resistance, local treatment with its suggestive potency, and the judicious use of sedatives, with recourse to a psychoanalyst familiar with these problems when necessary.

The incidence of psychosomatic disease has in itself a bearing on the problem. Rowntree,[13] discussing Army rejections for neuropsychiatric reasons, said that psychosomatic disease, which in peacetime had a high incidence among white persons but a very low one among Negroes, is increasing in both whites and Negroes. Menninger[14] quoted Surgeon General Norman T. Kirk to the effect that 50 per cent of all civilian patients of all doctors have symptoms derived from emotional disturbances. This author went on to point out that there cannot possibly be enough psychiatrists to handle the problem. Every person practicing medicine, he declared, should be as firmly grounded in psychiatry as in the other basic medical subjects and so be prepared to treat the minor personality disorders.

If Menninger's suggestions with regard to medical education are carried out, the medical schools will provide basic training in psychiatry for the surgeon of the future. The surgeon of today who lacks such training and wishes to equip himself to deal with psychogenic factors as they appear in his practice can do so through postgraduate courses and study of the available literature.

The following case reports illustrate many phases of psychosomatic relationships which the surgeon who wishes to save his patients much suffering, physical and mental, might bear in mind: the great variety of psychogenic symptoms which suggest to patients that they need an operation; the necessity of complete physical, laboratory, and roentgenologic examinations to eliminate or reveal organic disease; the necessity if somatic factors are eliminated of unhurried, careful, and sympathetic investigation of the possibility of psychic disturbances; if these are found, the need of tact and patience in dealing with them; and, finally, the rich reward the surgeon feels in the knowledge that he has avoided an unnecessary operation and has restored to health a patient who might have gone through life a victim of fears, anxieties, and debilitating symptoms.

CASE REPORTS

CASE 1.—Mrs. J. M., a white woman aged 43 years, of English ancestry, complained chiefly of pain in the right lower quadrant, vertigo, pressure in the chest, and bloating. A hysterectomy and appendectomy had been performed six years previously. One physician who had recently examined the patient had suggested an exploratory operation. A second had told her that there was no need for surgical intervention, that she was just imagining her discomfort and should forget about it.

My examination confirmed the absence of organic disease. Questioning elicited the fact that family discord resulted in much tension, with insomnia and a state of anxiety. Apparently the autonomic nervous system had chosen the colon as its seat of expression. The patient was certain that cancer must be developing.

Repeated reassurance of the absence of any organic disease and discussion of the causes of the patient's emotional tensions gradually relieved her fear of malignancy. She has become a healthy, much happier woman and has escaped becoming a victim of multiple operations.

CASE 2.—Mrs. F. L., a white woman aged 44 years, divorced, complained of pain and pressure over the goiter area, epigastrium and lower part of the abdomen, cardiac palpitation and oppression, vertigo, nausea, and irregular menstrual bleeding. In the past several months she had lost twenty pounds.

Seven years before, a cholecystectomy had been performed, and at that time the patient had been apprehensive of malignancy. After an uneventful recovery, however, her fears were allayed. Recently a cousin had died of cancer; her history had been almost identical with that of the patient. Both parents of the patient had died of cancer. During a recent examination elsewhere she had been abruptly informed that she, too, might have a cancer.

The patient looked extremely worried; she was thin and haggard, with tears in her eyes. A fine tremor of the hands was noted when she lighted a cigaret. The pulse rate was 100.

Physical examination showed nothing organically wrong except a uterine fibroid tumor the size of a large orange. The adnexa were not involved. Laboratory tests

gave normal results. The basal metabolic rate was plus 2 per cent and the electrocardiogram normal.

The patient was hospitalized for observation. On the evening of admission she complained of increased dyspnea and cardiac pain. It was apparent that these symptoms had followed receipt of flowers from her divorced husband, whom she still loved and admired. After she had been reassured and her attention directed to the obvious emotional reminder of her former husband, the symptoms subsided.

Each morning time was allotted for a discussion of the patient's emotional fears, and her attention was directed to the lack of symptom relationship between a uterine fibroid tumor and vertigo, nausea, cardiac palpitation and oppression, dyspnea, and goiter distress. One-quarter grain of phenobarbital was administered four times daily. The patient was reminded of her previous cancer phobia and its disappearance.

Each day a small but definite improvement was observed, so that when the necessary operation was performed eight days later the symptoms other than the abdominal pressure had all but disappeared. The resident noted on the chart two days before operation: "The patient feels better than at any time in the past several months." A supracervical hysterectomy was performed and the fibroid tumor, to which but few adhesions were found, removed. The pathologist's diagnosis was "fibroids and fibrosis of the uterus, chronic hyperplastic endometritis." The surgical convalescence was uneventful. The patient lost the appearance of fear, her appetite improved, and she even became cheerful. Her attention was repeatedly directed to the fact that all her symptoms except the pressure in the lower part of the abdomen had vanished before operation and so could not possibly have been related to the tumor.

Comment.—The importance of clearing up the psychosomatic symptoms *before operation* cannot be overemphasized. Clearly, persistence of such symptoms after surgery would have led this patient to believe that a disease process of some sort had been overlooked at operation. Such an occurrence took place in the following case.

CASE 3.—Mrs. R. F., a white woman aged 39 years, of German ancestry, complained of precordial pressure and dyspnea, which were especially severe when she was nervous, and of abdominal pain and fullness, with gas on the stomach varying as to location and intensity. These symptoms had been present for several years, and she was afraid of cancer. The history disclosed that she had always been nervous and sensitive and had feelings of insecurity. Eight months before, a competent surgeon had operated for bilateral hydrosalpinx, removing the fallopian tubes and performing uterine ventral suspension. A letter from this surgeon did not mention nonorganic symptoms continuing postoperatively.

The patient insisted that an exploratory laparotomy be performed. She was convinced that an abdominal cancer had been overlooked.

Complete physical, roentgenologic, and laboratory examinations gave negative results. The patient weighed 110 pounds, although she should have weighed about 130. Since she had emotional difficulties which required psychotherapy, she was referred for such therapy. Within a few weeks her symptoms, including the cancer phobia, had vanished and she had gained twenty-three pounds. Today she is a healthy, happy person and has avoided useless and traumatizing multiple operations.

Comment.—This patient had emotional and nervous factors whose resolution appeared to be beyond the scope of the surgeon, and she was

therefore referred to a psychiatrist. The clinician and surgeon should remember Hinsie's warning:[15]

> *The aim of psychotherapy from the standpoint of the nonspecialist should be restricted to the treatment of conscious material.* Many of the patients whom he sees can be cured by psychotherapy of that part of the mind known as the conscious. The unconscious, that is, the hidden part of the mind, is the province of the specialist, is the province of those who are well familiar with the structure and function of the unconscious.

CASE 4.—H. F. B., a white man aged 52 years, married, a lumber salesman, for the past eight months had had pain in the upper part of the abdomen. Food might aggravate the distress but just as frequently served to allay it. The type of food seemed to have no bearing on the situation. Belching and bloating were frequent. During the previous six months the patient had lost twenty-one pounds. Insomnia occurred repeatedly. Six years before, after a diagnosis of cholelithiasis, chronic cholecystitis, and interval appendicitis had been established, a cholecystectomy and appendectomy were performed.

The patient's father and paternal grandmother had died of gastric carcinoma, and a paternal aunt had died three years after a mastectomy for a malignant tumor. The patient insisted that he, too, must have a cancer because of the abdominal symptoms and loss of weight.

Examination disclosed definite epigastric distress, but no mass was palpable. Roentgenograms of the gastrointestinal tract showed nothing abnormal except a slight deformity of the duodenal bulb, which the roentgenologist interpreted, not as an ulcer, but rather as the result of adhesions to the gall bladder previously removed. An electrocardiogram and basal metabolic studies gave normal results. Routine examination of the blood, stool, and urine showed nothing abnormal.

The patient was informed that no organic cause for his symptoms had been found. He demanded an immediate exploratory laparotomy because he was sure there was a tumor which had not been revealed by the films. Surgical intervention, we assured him, was not indicated.

Detailed inquiry revealed several factors which suggested an emotional rather than a somatic causation of his symptoms. His family's history of malignancy was definitely preying on his mind. The financial depression had all but wiped out his modest fortune, and his business had fallen off. His wife was in the throes of the menopause, with its accompanying depression, flushes, and extreme irritability. His 83-year-old mother lived in his home and needed almost constant attention.

The relation of the patient's numerous anxieties and worries to his abdominal complaints via the autonomic nervous system was explained. His wife was given the necessary estrogen therapy and soon was much improved. The mother was sent to live with a sister. The importance of accepting reality and making the best of it was impressed on the patient during a number of visits to the office. His attention was repeatedly directed to the fact that there was no physical cause to account for his symptoms. The futility of an exploratory operation was reemphasized.

The abdominal discomfort gradually decreased, with only an occasional flare-up. The twenty-one pounds lost were regained, plus an additional five pounds. The insomnia disappeared after several weeks and has not recurred. When last observed, the patient had been symptom-free for many months. Now and then he would have slight abdominal distress or a brief period of belching, which could invariably be traced to an emotional upset. His wife, now in excellent health herself, recently stated that he was feeling fine and apparently had decided that no malignant growth existed.

Comment.—In this case an exploratory operation might well have resulted in serious emotional trauma. The original symptoms would undoubtedly have persisted, as in Case 3, and might even have been aggravated.

CASE 5.—R. K., a white man aged 34 years, of Irish ancestry, an office administrator, complained of pain after eating, sensitivity in the lower left part of the abdomen, and constipation, all of many years' duration. The distress might disappear from the abdomen, only to recur several hours later, and might even migrate to the chest. Fatigue was always present. The history disclosed that the patient had been nervous for many years. Various physicians had prescribed rest, medication, and vitamins, but these gave little help. Even when the patient was on vacation the symptoms persisted. He was convinced that he had a tumor which could be discovered and removed only by surgical operation. He had been referred to me by a patient who had had a cholecystectomy performed, with an uneventful recovery and convalescence.

Complete physical examination and routine laboratory studies were carried out. In addition, roentgenograms of the gastrointestinal tract and gall bladder, an electrocardiogram, and basal metabolic studies were undertaken. The results were negative.

Merely to inform the patient that his symptoms had no organic cause would have been to leave his symptoms unchanged. It was essential to go a step farther in the investigation. The lead of nervousness recorded in the history was followed, and it was learned that the patient had always been upset emotionally after criticism, chastisement, or ridicule. When he was a boy his father had dominated him and had been critical and unkind. Visits to the home of his parents were still accompanied and followed by abdominal distress. In high school, in college, and at work, censure, reproval, fault finding, and too critical analysis of his accomplishments invariably precipitated abdominal distress or a burning sensation at mealtime.

The patient's intelligence would have been insulted if he had been told that there was nothing wrong, that he should go home and forget his symptoms. The fact that no organic cause could be found to explain the presence of pain did not mean that the pain was not present. Certainly surgical intervention was contraindicated.

On several subsequent visits to the office the patient's attention was directed to the fact that his discomforts appeared to be directly related to emotional reactions of inadequacy. He had been frustrated in his relations with his father, with his teachers, and now with his office associates. Feelings of frustration were present whenever he felt that unnecessary or unjust criticism was being leveled at him. He invariably blossomed under praise. A feeling of inadequacy had been built up as a result of the repeated emotional trauma.

It was explained to the patient how his gastrointestinal tract was involved by the autonomic nervous system in the expression of his emotions. He was guided toward a constructive acceptance of criticism. He was encouraged not to allow criticism to register as an emotional blow, to take it as a passing remark rather than as a personal affront.

CASE 6.—Mrs. C. E. R., a white woman aged 67 years, of Irish ancestry, complained of nausea and of pain in the abdomen shifting from the upper quadrants, especially the left, to the lower quadrants. These symptoms had been present for several years but had been more pronounced the past four or five months. The patient said she frequently felt tense, "as though in a vise."

The patient was well nourished and not acutely ill. Physical examination revealed vague tenderness over the right lower quadrant and a large smooth mass to

the right and independent of, but adhernt to, the uterus, probably an ovarian cyst. Complete roentgenologic studies of the gastrointestinal tract and the gall bladder gave negative results, as did all laboratory investigations.

With some hesitation the patient revealed that she had had coitus with her husband several months before, after ten years of abstinence. She felt certain that something had happened in the vagina, a tear or inflammation. Shortly thereafter she consulted a physician, who discovered a mass in the lower part of the abdomen and informed her, in jest but with a straight face, that she must be pregnant. After successive examinations he told her that the mass was growing larger, but he made no further mention of pregnancy.

With trepidation in her voice, the patient said she was sure that she was pregnant, with a freak pregnancy, and that the doctors would not tell her. She recalled reports that children of 5 and 9 years had become pregnant—why not a woman of 67? "And that would be awful, doctor!" She admitted that she had always disliked coitus. Considerable time and patience were taken to explain that no pregnancy or vaginal lesion existed, and during the next several days the patient showed great improvement. There had been no symptoms from the ovarian cyst, and the psychosomatic symptoms disappeared. One week later a periovarian cyst 15 cm. in diameter was removed, and the postoperative course was remarkably free from complications. The patient was discharged thirteen days later, feeling healthier and happier than she had been in years. She has since been seen several times and continues in good emotional and physical health.

CASE 7.—Mrs. E. R., a white woman aged 36 years, an American of Lithuanian ancestry, complained of pain in the right lower quadrant and the lower part of the spine. She believed that this pain was due to an ovarian cancer. Burning pains, like those of rheumatism, occurred in the upper part of the chest, both front and back. There were urinary frequency and diarrhea, and belching occurred after meals. The patient had frequent attacks of cardiac oppression and palpitation, with vertigo. She had a fear of impending disaster, that she might collapse and no one be present to give aid. She stated that she had always been nervous but that during the past two years the symptoms listed had become much more severe.

The history disclosed that two years earlier a sister had died and that shortly thereafter a second sister had committed suicide. From that time the patient had frequently been troubled with insomnia and with unpleasant dreams of these sisters and of the cemetery where they were buried. Her mother had impressed her with the superstition that dreaming of the dead, especially in the immediate family, meant that another death in the family was sure to occur. The patient was convinced that she would be the next to die, and she had frequent fits of crying and depression.

Complete physical examination revealed no pathologic change except a large cyst of the right ovary. This cyst could not possibly have accounted for the long list of symptoms. Laboratory examinations revealed nothing significant. Complete roentgenologic studies of the gall bladder and gastrointestinal tract gave negative results except to show moderate spasticity in the descending portion of the colon.

The lack of physical findings except for the ovarian cyst was explained to the patient, as was the impossibility that her many symptoms could be related to the cyst. The fact that her disability was out of proportion to the disease present was emphasized. A number of consultations were needed to convince her that her symptoms had no somatic foundation but originated in her basic fears, conflicts, and apprehensions. Time and patience were taken to explain that the autonomic nervous system influences the heart, stomach, colon, bladder, and other pelvic organs, and that anxiety and worry had resulted in certain reactions in these organs,

producing the symptoms of which she had complained. Gradually, after reassurance and repetitive discussion of her emotional fears, her various complaints disappeared.

The ovarian cyst, which proved to be 13 cm. in diameter, was then removed, and the patient made an uneventful recovery. The only symptom which remained was occasional pressure and pain in the right lower quadrant. Both the patient and her husband state that they cannot recall when she has been as healthy, happy, and cheerful.

Comment.—Obviously the bizarre symptoms could not have been caused by a simple ovarian cyst, the only lesion present. To have operated before eliminating the psychosomatic symptoms would have been to risk continuation of these symptoms and possibly another operation because of the cancer phobia. The patient's new understanding of the psychodynamic implications served to clarify the basis of her fears and thus to eliminate them.

SUMMARY AND CONCLUSIONS

Psychosomatic symptoms in patients who consult the surgeon must not be overlooked or ignored. They are as real and as significant as are the symptoms which are organic in nature. They are the expression of emotional disturbances, manifested via the autonomic nervous system as organic complaints. To tell the patient to forget them, and to do nothing to relieve them, is to neglect a vital phase of the art of healing.

Psychogenic symptoms frequently simulate the effects of organic, operable lesions. The surgeon, therefore, sees many patients who present them. By recognizing them for what they are—neither evidence of a somatic disease process unverified despite physical and laboratory investigations, nor evidence of a true neurosis—he will avoid needless surgical procedures and save his patient much mental and physical sufferings.

When a patient is found to have an operable lesion, but one which could not possibly be the cause of all his many complaints, it is extremely important to clarify the unrelated symptoms before the necessary surgical procedure is undertaken. Otherwise these may well persist after operation, and it will be a difficult task indeed to convince him that he does not have a lesion which was overlooked at operation.

Cases cited from a surgical practice illustrate some types of psychosomatic symptoms which a surgeon is apt to encounter, and detail a variety of causative factors and methods of dealing with them in order to secure for the patient improved mental and physical health.

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IODINE AND THYROIDISM

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HISTORICAL

BERNARD CURTOIS while experimenting in the extraction of alkali from seaweed, discovered iodine (1811).

After Fyfe had isolated iodine from sponges, Jean Francois Coindet (1820), of Geneva, maintained that the element is the active constituent of burnt sponge and is effective as a remedy for diseases of the thyroid.

Trausseau (1868) experimented with the use of tincture of digitalis instead of iodine, in the treatment of goiter.

Plummer (U.S.A.) was the first to popularize the use of iodine in exophthalmic goiter.

Charles Edouard Brown-Séquard, in 1889 (antedated by Ruysch, Johannes Müller, and others), made an epochal report to the Biological Society of Paris. His experiments indicated that the ductless glands furnished substances to the blood which influenced the organs of the body to a pronounced degree.

In 1895, Magnus-Levy fed dried animal thyroids to normal men and made the original observation that their metabolic rate was considerably increased.

From about 1893 onward, he used the Zuntz-Geppert technique in his estimation of the metabolic rate, with the realization that the effect of disease on metabolism could not be appraised without the study of normal controls.

It thus became evident that the gland must contain a potent chemical substance able to influence many other organs. Kocher prophetically suggested that this substance might contain iodine, which was known to have beneficial effects when given to cretins. Somewhat later (1896) Baumann discovered that the thyroid contained large amounts of iodine in combination with organic substances, chiefly globulin. This he denominated iodothyrin (later thyroiodine) and showed that from the purest thyroiodine 9.3 per cent of iodine could be obtained in crystalline form.

As a result of the work of Kendall (1913-1919) and Harington (1926-1930), a pure chemical substance was finally isolated from the thyroid gland. Kendall named it "thyroxine." When this substance was injected into men (or beasts) the symptoms of hyperthyroidism were produced.†

Received for publication, Nov. 2, 1944.

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†Journal of Experimental Medicine, 1915.

HISTOLOGY AND PHYSIOLOGY

It must be recalled that the units of thyroid tissue are glandular vesicles or acini which are lined by a layer of epithelial cells. They remove iodine from the blood and convert it into an active hormone. A constituent of this hormone, thyrotoxine, was identified and later synthetized.

Among the factors which influence the functional activity of the thyroid are the amount of available iodine for synthesis and the pituitary thyrotropic hormone. The substance formed by the thyroid cells passes into the lumen of the vesicle where it is stored as a colloid. This is resorbed through the thyroid cells and sent into the blood stream.

The histologic structure of the gland is a gauge of its functional activity. Inadequate activity, or overactivity, may consequently be evidenced by histologic examination. Not only is the activity of the normal thyroid tissue cyclic, but in diseased thyroids different parts of the gland may show different degrees of function or actual dysfunction.

Dr. Joseph G. Hamilton, Dr. Mayo H. Soley, and Dr. Carl B. Eichorn, of California University, described a method by which it is possible to correlate the deposition of administered iodine in the thyroid with the histologic structure of the gland. They wrote as follows:

> Two days after the administration of a radioactive isotope of iodine the thyroids were extirpated and sections were prepared from the glands. The sections were placed against photographic plates on which the beta radiation from the accumulated radio iodine produced areas of darkening. These images made a pattern of the distribution of the stored radio iodine in the sections of thyroid tissue. Each exposed film was compared with its corresponding section under a microscope. This technique was employed to compare the deposition of the administered radio iodine with the histologic structure of the thyroid tissue obtained from five patients with nontoxic goiters, two patients with carcinoma of the thyroid, and two patients with hyperthyroidism. In all the varieties of thyroid tissue examined the areas of hyperplasia were found to have the greatest ability to concentrate the administered radio iodine. This phenomenon was most clearly shown in the glands of patients with nontoxic goiters. . . The selective accumulation of radio iodine by hyperplastic thyroid tissue indicates that this radio-active element may be of therapeutic value in hyperthyroidism.*

It has been shown time and again that the follicular cell is the unit of thyroid function and may undergo, like all large and minute tissue entities, hypertrophy and hyperplasia with increased activity. This unit appears to be the prime factor in thyroidal physiology and pathology. Under normal conditions the cell is cuboidal, with clear cytoplasm and a nucleus situated near its base. This appearance is subject to slight variations largely dependent on the degree of glandular activity. At rest the cell is readily stimulated (particularly by iodine)

*Publication in Pharmacology, University of California.

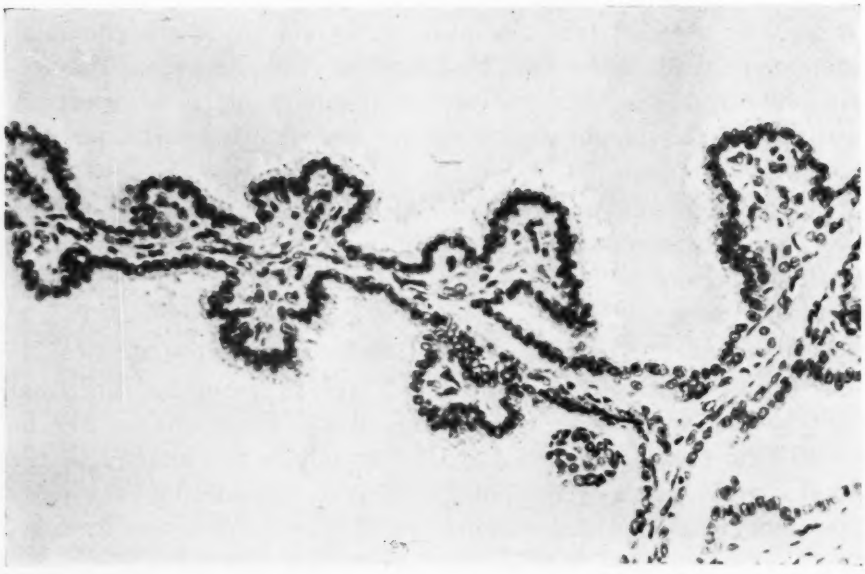

Fig. 1.—A 27-year-old white man with a basal metabolic rate of plus 49 after iodine therapy. Pathology: There is marked hyperplasia of the epithelium. The cells lining the follicles are tall, and many papillary infoldings extend into the lumens. There is diminution of colloid, and the margins along the cell borders are "scalloped." (U. S. Army Medical Museum Negative No. 75852, Pathology of the Thyroid Gland, Army Medical Museum, February, 1944.)

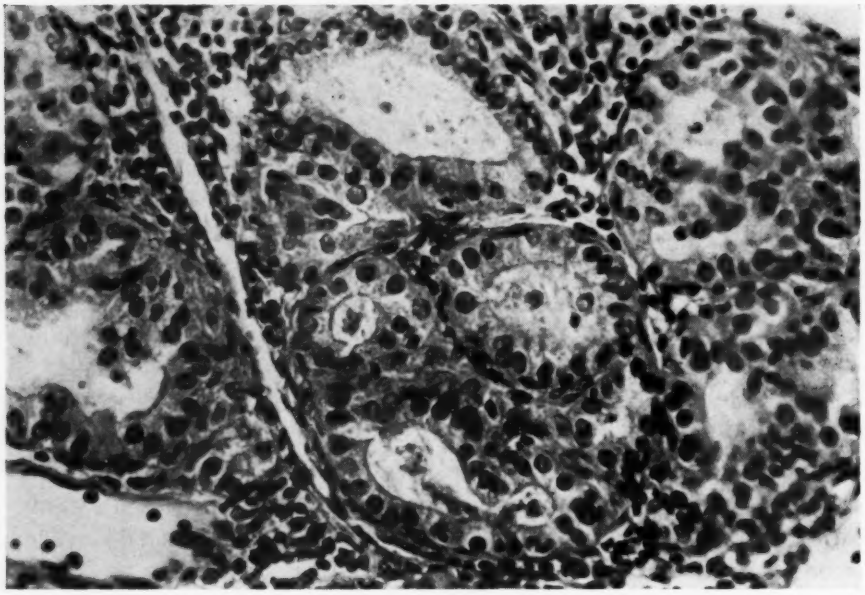

Fig 2.—A 22-year-old white man who had a basal metabolic rate of plus 65, which fell to plus 31 after iodine therapy. Pathology: In most of the follicles colloid is diminished or absent. The follicular epithelial cells are enlarged and tall. Most of the follicles are evenly rounded, and little papillary projection is seen. In a few areas the epithelium is flattened and no colloid is present in the follicles. There is a lymphocytic infiltration throughout. (U. S. Army Medical Museum Negative No. 75851, Pathology of the Thyroid Gland, Army Medical Museum, February, 1944.)

and in consequence becomes columnar, with its cytoplasm granular and its nucleus elevated. This mutation likewise occurs through glandular activity which obtains at puberty, menstruation, and pregnancy. A decreased intake of iodine results in an increased colloid storage. The cell then loses its cuboidal form, becoming flat. The cytoplasm is almost indistinguishable and the nucleus, magnified, appears to occupy the cell in its entirety. This has been denominated the "inactive or resting stage." In an advanced phase the nucleus is faintly visible, the cytoplasm poorly stained, and the cell properly flattened.

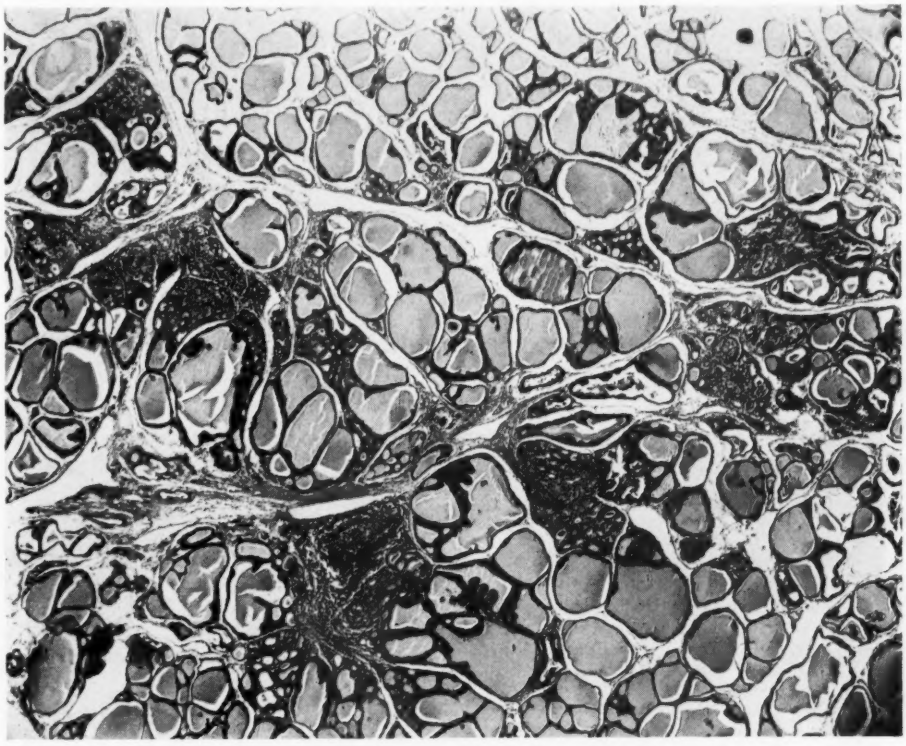

Fig. 3.—A man 31 years old, with a plus 70 basal metabolic rate, received iodine for seventeen days prior to surgery. Pathology: This section shows alternating areas of hyperplasia and involution. Compare the height of the flattened epithelium of the involuted follicles with that of the tall hyperplastic cells. (U. S. Army Medical Museum Negative No. 75854, Pathology of the Thyroid Gland, Army Medical Museum, February, 1944.)

The variety of epithelium lining the follicles is the most important index of thyroid activity. It is clearly axiomatic that: (1) Tall columnar epithelium resorbs hormone from the follicular lumen and discharges it into the blood stream; (2) high cuboidal epithelium actively produces colloid; (3) low cuboidal epithelium produces colloid slowly; (4) low, flat epithelium is inactive. (See Figs. 1 to 5.)

The height of acinar epithelium, therefore, acts as a measure of functional activity and in all probability also as a functional measure of the thyrotropic hormone of the pituitary. Marine and Lenhart, writ-

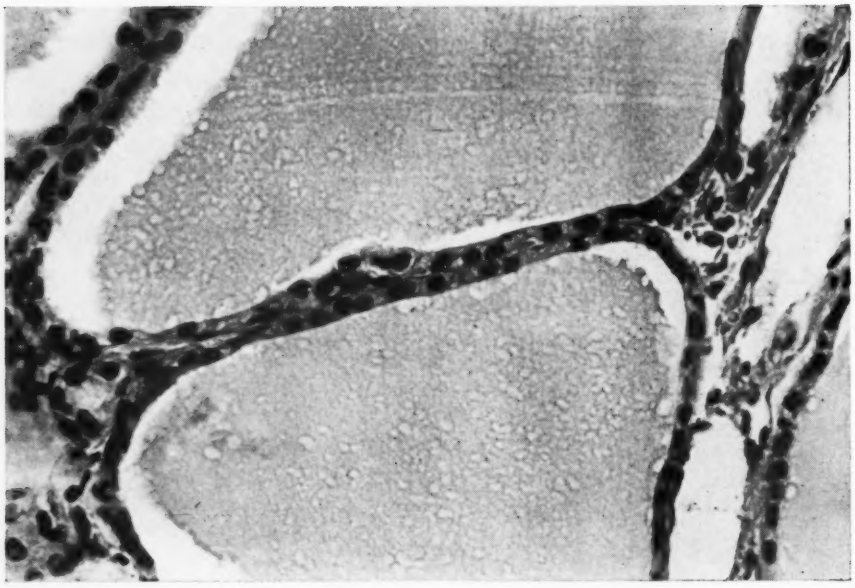

Fig. 4.—Flattened epithelium of involuted follicles seen in Fig. 3 (U. S. Army Medical Museum Negative No. 75825, Pathology of the Thyroid Gland, Army Medical Museum, February, 1944.)

Fig. 5.—A 39-year-old white man. Basal metabolic rate was plus 45. Pathology: The follicles and their epithelium show all stages of transition from the hyperplastic to the normal. The unusually large follicles distended with colloid are hyperinvoluted. In some areas the epithelium is abnormal and resembles the types seen in some adenomas. (U. S. Army Medical Museum Negative No. 77415, Pathology of the Thyroid Gland, Army Medical Museum, February, 1944.)

ing of the thyroid-pituitary relationship, concluded that the thyroid secretion affects the pituitary to the same degree as the thyrotropic principle of the pituitary affects the thyroid* Herring found that the neural posterior lobe of the pituitary is also involved in hyperthyroidism.†

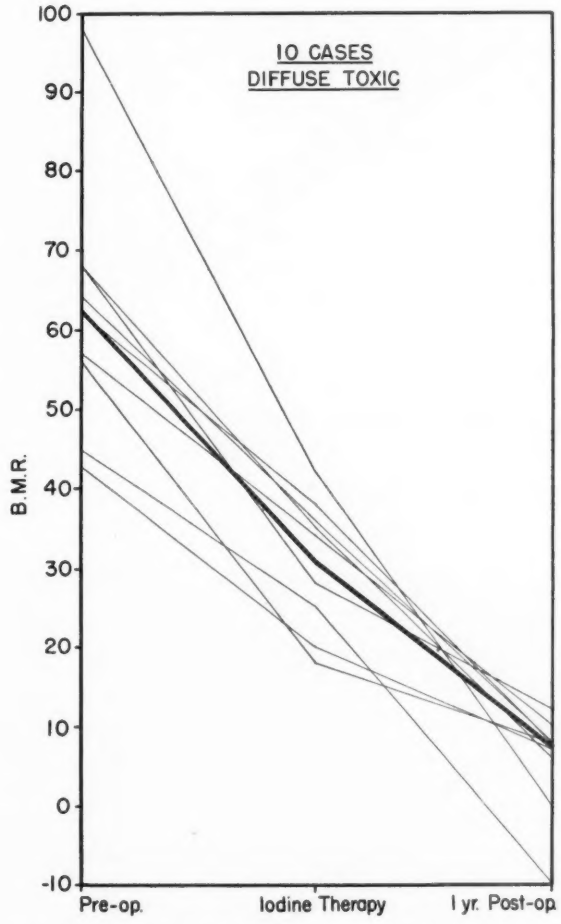

Fig. 6.—Graph of ten typical cases of diffuse toxic goiter (hyperplasia) illustrating the effect of iodine therapy and surgery on the basal metabolic rate.

It is obvious that the iodine content of the gland is the determinant factor in its activity; if the total is adequate there is no dysfunction but if it drops below a specific level, accelerated activity and hyperplasia are exigent for physiologic requirements.

It is of interest to note that the thyroid glands of fetuses and of newborn infants are iodine-free. The gland in herbivora has a high iodine content, while that of carnivora has the lowest iodine content (Baumann, Ross, and Oswald).

*Archives of Internal Medicine, 1911.
†Proceedings of Royal Society of Medicine, 1921.

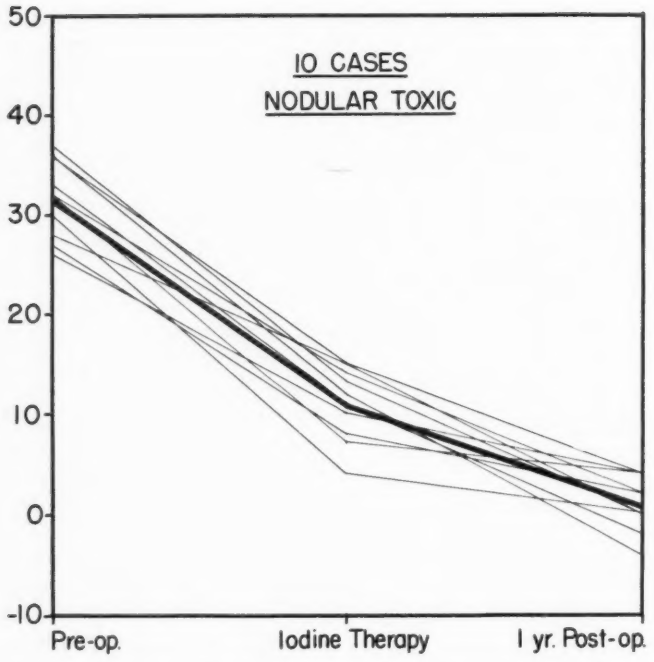

Fig. 7.—Ten cases of nodular toxic goiter (adenomatous) illustrating the results obtained in reduction of basal metabolic rate after preoperative iodine administration followed by surgery.

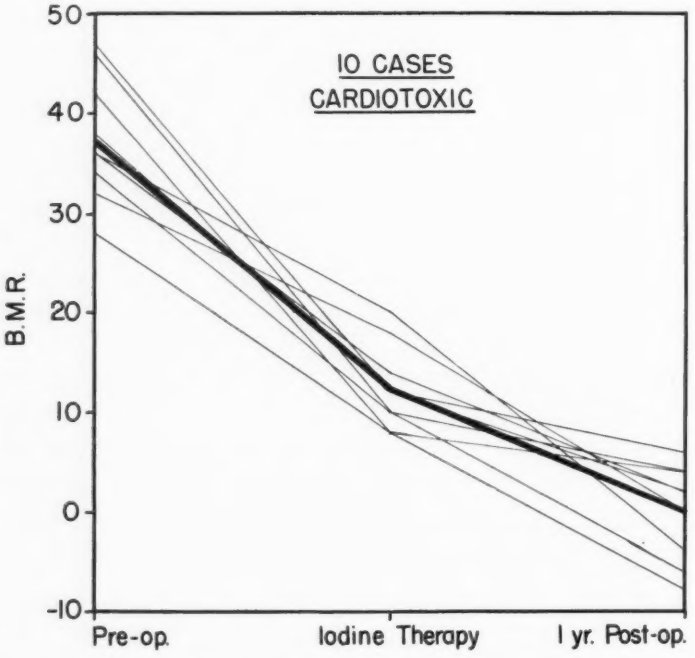

Fig. 8.—Reduction of basal metabolic rate in ten cases of cardiotoxic goiter (Hertzler) after iodine therapy and surgery.

The basic function of the thyroid is the production of thyroxine to maintain the metabolic rate higher than it would be otherwise and through variation in activity to alter the metabolic rate in accordance with physiologic needs. Recent investigations have shown, however, that the symptoms of increased thyroid activity caused by hyperplasia of the gland are not invariably accompanied by a raised basal metabolic rate. (See Figs. 6 to 9.)

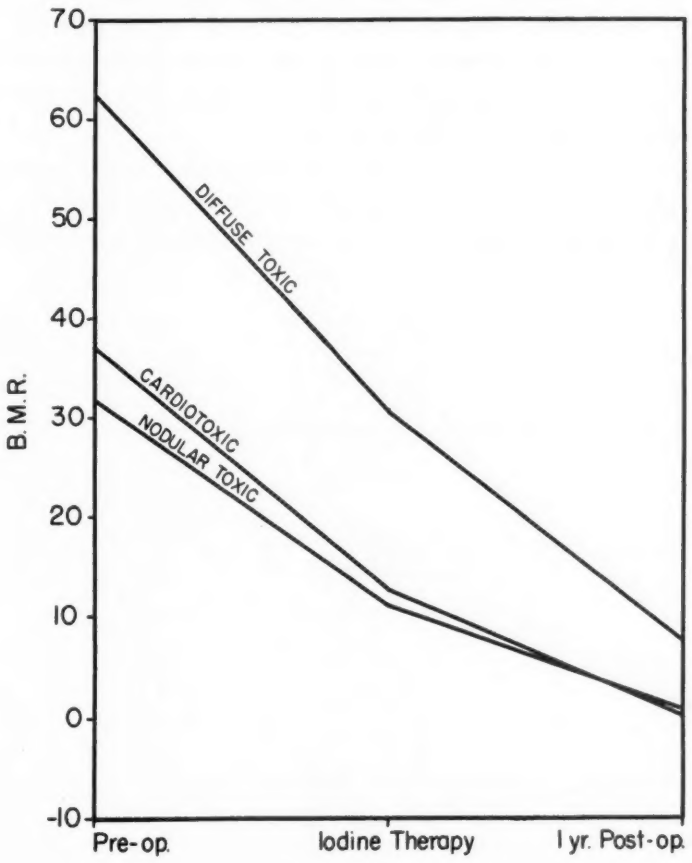

Fig. 9.—Composite graph of Figs. 6, 7, and 8.

With a total cessation of thyroid function the oxygen consumption or basal metabolic rate falls to 40 per cent. Incidentally, 1 mg. of thyroxine causes an increase in metabolism of about 1,000 calories in a normal person.

The thyroid hormone is present in its highest concentration in the thyroid gland but has been found in nearly all body tissues, including the skin, and in the body fluids. In the blood 60 per cent of iodine is alcohol-insoluble (thyroxine) and 40 per cent alcohol-soluble. This balance, however, is disturbed in thyroid disease; in hyperthyroidism, for example, there is a relative increase in the alcohol-insoluble fraction.

The normal thyroid contains 10 mg. of iodine at a concentration of 40 mg. per cent by weight. This is largely present in the colloid. The normal iodine content of the blood is 12 micrograms per cent. This indicates that the normal blood contains 120 parts of iodine per billion. The blood iodine is increased in patients with hyperthyroidism and is less in normal persons. (The normal daily iodine requirement is about 0.2 mg. per day; the average amount actually taken on ordinary diets is about 1.0 mg. per day.) After administration of iodine there is an increase in the iodine content of the thyroid. Administered iodine becomes stored and firmly bound within the thyroid almost instantaneously, but in some obscure form, not as thyroxine, for synthesis of the latter requires a number of hours (Fig. 10).

It is known that iodine and thyroid function are interdependent because the gland is the principal storehouse of the element. So far as is known it is the only organ capable of elaborating an iodine-containing substance.

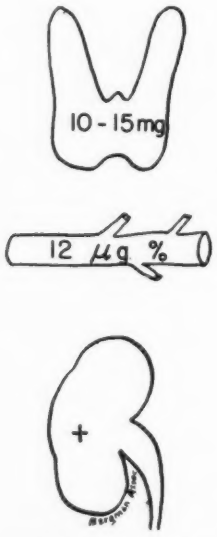

Fig. 10.—Iodine content of thyroid, blood, and urine in a normal individual.

The fundamental features of iodine metabolism in exophthalmic goiter are the following: (1) In untreated patients the thyroid gland iodine is lessened; (2) the blood iodine is usually increased in untreated persons; (3) the urinary excretion of iodine is ordinarily increased; (4) exophthalmic goiter reveals a progressively decreasing iodine balance. However, patients with toxic nodular goiter present an even greater negative iodine balance due to a greater urinary excretion, and immediately following thyroidectomy a rise occurs in the blood iodine of noniodinized patients, whereas there is a decrease in those treated with iodine (Figs. 11 and 12).

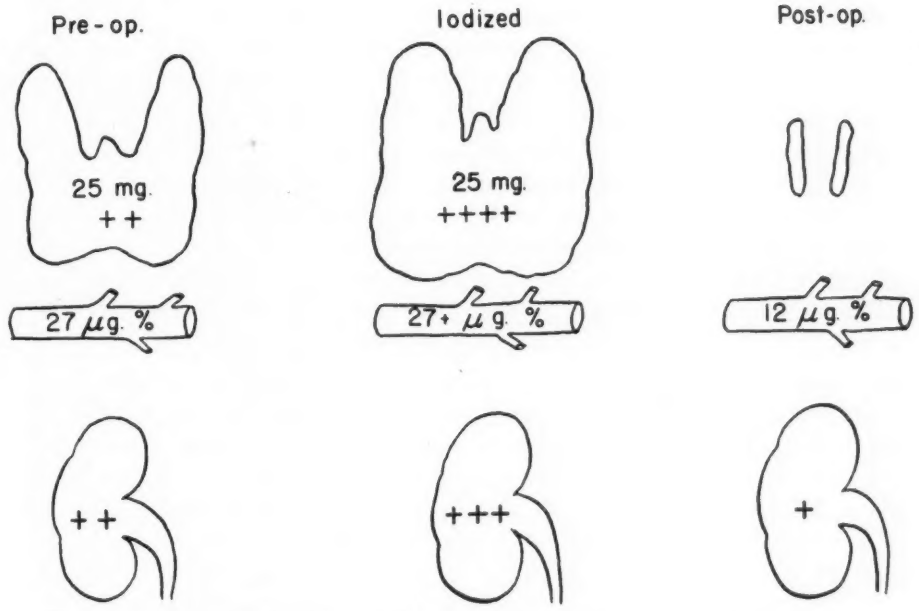

Fig. 11.—Iodine metabolism in individuals with diffuse toxic goiter (hyperplasia).

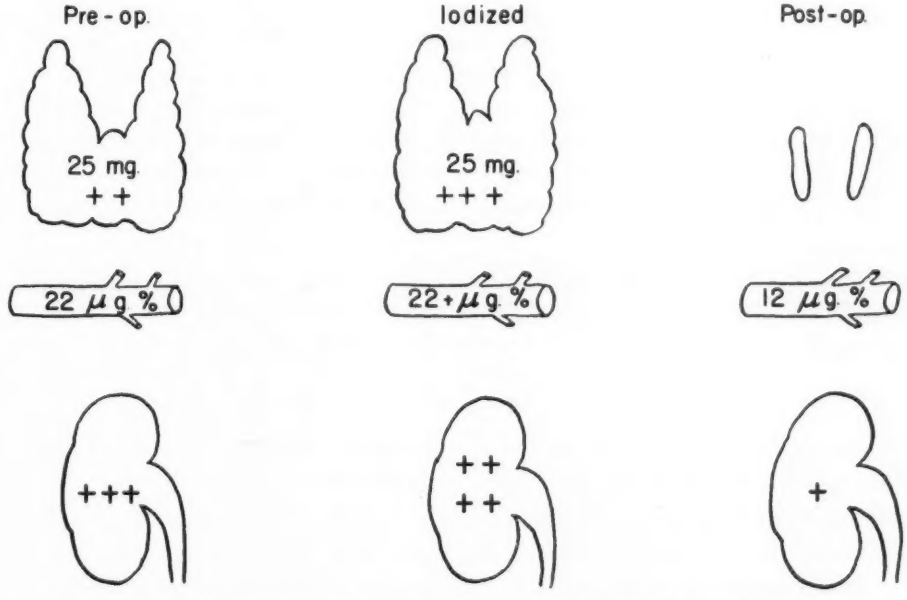

Fig. 12.—The iodine content that prevails in a nodular toxic goiter (adenomatous), preoperatively, before and after iodinization, and postsurgically.

PATHOLOGIC PHYSIOLOGY

A dissident view concerning the cause of hyperthyroidism is that it is not always due to an accumulation of iodine. The thyroid gland, it is argued, normally contains a certain amount of iodine stored as an inert compound. A gradual disintegration takes place, according to the requirements of the animal economy. This assumption has many physiologic parallels in fibrinogen, mucinogen, glycogen, and all other substances by which a material is stored inert until required. It is common knowledge among physicians that the amount actually present, though not great, is fairly constant in health; that the intake is necessarily variable and precarious; and the normal excretion so small that, in our day, the matter remains purely conjectural. It is obvious, then, that some physiologic provision should be made for the preservation and retention in the body of such an essential element, the supply of which is so precarious. Succinctly stated, the same iodine is used repeatedly, being freed from the thyroid storehouse to perform its functions, one of which is that of acting as a lime carrier, and returning empty to the thyroid where it again enters into suitable combination and is again stored until required. Under these conditions, to pursue this theory further, it seems probable that hyperthyroidism is the result of an excessive discharge of the reserve iodine into the system by the chemical disorganization of the substance which normally holds it in storage. The iodine thus cast into the system produces hyperthyroidism. Thus, a sudden explosion in the iodine stores of the thyroid gland is all that is needed to flood the system with iodine and start the afore-mentioned disease. This is probably what occurs when the disease is started by fright or sudden shock. Psychic trauma and emotional upsets often start symptoms of toxicosis doubtless owing to the interdependence of the diencephalon and the pituitary. Nevertheless, it is known that hyperthyroidism is responsible for the stimulation of psychic emotions.

It is obscure by what means iodine is normally set free from the thyroid gland, though it is assumed that it is governed by laws of chemistry which are under the control of nervous impulses.

THERAPY

Therapeutic effects of iodine are extremely variable. There is an optimum amount suitable for different patients.

Iodine administration brings about a striking amelioration of the condition but the improvement disappears when the iodine is withheld. If iodine is continued indefinitely the disease is milder than otherwise, but it is not of shorter duration.

Some thyrotoxic patients grow progressively worse under iodine medication because the amount of iodine administered is actually inadequate. As soon as the optimum increase of iodine is found, the syndrome, with

the associated disturbed metabolism, is checked and regresses. This does not carry the implication that it is best to begin treatment with large doses of iodine. It is advantageous to start with a small dose, 10 mg. of Lugol's solution, for example, and then to observe the reaction. If this proves ineffectual the dose should be rapidly increased until the optimum amount is found for the specific patient. It is well to bear in mind, incidentally, that on rare occasions an apparently inadequate dosage may induce a refractory phase in the therapeutic regimen.

There is still a sharp difference of opinion among clinicians as to what constitutes a small dose of iodine. It is estimated that 6 mg. daily is a needful amount of iodine to induce maximum colloid accumulation in the normal thyroid gland. Smaller doses, it has been shown, appear to be insufficient to induce a maximum storage. It is clear, therefore, that 6 mg. daily is a sufficient dosage in the treatment of thyrotoxic goiter. Many investigators, however, have found that this physiologic dosage frequently proves ineffective.

Admittedly, a certain number of thyrotoxic patients, for occult reasons, appear to be iodine resistant. The resistance is not solely against iodine. It is also true of the prolonged use of various glands of internal secretion.

It has been maintained that the refractory influences are induced either by the formation of substances which neutralize the utilized iodine, or by antihormones, if endocrine substances have been given. This is brought about by a self-regulatory mechanism which counteracts the effects of the substance used therapeutically.

It is conceivable that some patients who are "lugolized" for a time become intractable to iodine. There are those, too, who are iodine resistant under all circumstances.

It has been maintained that the intractability in question, which occurs after prolonged use of iodine, is due to prolonged medication, with a consequent exhaustion of the thyroid, evidenced by the total disorganization of the parenchyma of the gland noted macroscopically and microscopically. The gland is consequently unable to assimilate iodine and thus there is a failure of therapeutic effect.

Means wrote that there is no true refractoriness to iodine and that the only patients who really do not respond are those who are not thyrotoxic, or if so, are already iodinized. Of all patients in his series, only 3 per cent apparently failed to respond; this small group was explained by a rapid increase in severity of the disease occurring at the time the iodine was given. A poor response to iodine, he holds, is indicative of a poor surgical result. In ward cases of the Massachusetts General Hospital, over a ten-year period, reported by Means, the mortality of patients who responded well to iodine (97 per cent of all cases) was 1.1 per cent; in those who did not respond well (3 per cent of all cases) the mortality was 27.3 per cent.

The physiologic and chemical role of iodine in thyrotoxicosis is still shrouded in a veritable theoretic fog. This is also true of the frequent return of the syndrome to its previous or more advanced stage after a few weeks of iodine medication. And still seeking a scientific explanation is the answer to the question: "Why does iodine induce a specific response in thyrotoxicosis—a response which is absent when iodine is administered to normal persons?" This response in thyrotoxicosis makes confusion more confounded in that it is absent in experimental hyperthyroidism when thyroid extract is used in men and beasts, as was shown by Carson, in 1928.

The following factors must be considered in an attempt to elucidate the multifarious effects of iodine administration in thyrotoxicosis:

1. De Ligneris, Marine, and many other investigators, have given this aspect of the quest profound study. It is now widely accepted, in fact, axiomatic, that iodine increases the alveolar colloid content. This substance apparently thickens, and thereby distends the walls of the repository, of which the cells and their nuclei flatten and elongate in the process. The interstitial cells are strikingly diminished in size and number.

2. In the diffuse thyrotoxic parenchymatous goiter the colloidal iodine is quantitatively inadequate and excreted into the blood, and ultimately, into the lymph stream. The iodine reserve of the thyrotoxic gland is consequently lessened and obviously the blood iodine is relatively increased. However, the glandular iodine is largely ionized and inorganic, while the organic fraction in the blood is increased. It is the ionized inorganic iodine which is thyrostimulant, as shown by Saegesser, in 1932. It may be argued that under favorable, or unfavorable, regional and physiologic influences the stimulation may, in a manner of speaking, cause the gland to run amuck.

3. Iodine when supplied to a thyrotoxic gland is adequately stored and utilized to a degree where physiologic needs are satisfied. The relation of the various fractions of thyroid return to normal, the colloid is again in reserve, and there is stabilization of thyroidal function. This is largely proved by the clinical behavior of the patient and specifically by the absence of thyroidal manifestations. The soft, elastic consistency of the gland is changed to a distinctive firmness consequent upon the alveolar storage of colloid. These units, as previously stated, become distended to capacity. This is what is known as the "thyroid response" to the ingestion of iodine. *It is a physiologic phase.*

4. Another well-nigh paradoxic effect frequently noted is not only the recrudescence, but the augmentation, of thyroidal symptoms despite the continued use of iodine. An apparently valid explanation is that the element, having accomplished its physiologic purpose, is no longer required, except in the mere maintenance of physiologic function.

When the increased iodine supply is kept up the effect goes into reverse, becomes pathologic, with a train of toxic symptoms.

5. Iodine therapy is less effective in thyrotoxic nodular goiter than in the diffuse parenchymatous variety. This is because the degree of cellular hyperplasia is greatly reduced in the latter condition. The large colloid nodules present are only moderately influenced by iodine administration. They do not readily yield their large thick colloid reserve as in the easy manner of the alveoli in the diffuse parenchymatous form of goiter. It is thus clear why thyrotoxic nodular goiter responds to a less degree to iodine than the diffuse parenchymatous forms, in which the cellular elements are hyperplastic and overactivated.

6. Iodine is not a cure for thyrotoxic goiter, but in most instances induces a resting phase so that the patient is "safe for surgery."

7. Prolonged iodine medication, especially with high dosage, frequently results in thyrotoxicosis.

8. Again, this may induce a refractory state.

9. Nevertheless, iodine medication is indicated in all varieties of thyrotoxicosis.

10. The ideal medicament for thyrotoxic patients with cardiac manifestations is iodine. Thiouracil,* recently discovered, may have some value as a depressant of thyroid function. "The daily administration of 1 to 2 Gm. of thiourea or of 0.2 to 1 Gm. of thiouracil to hyperthyroid persons," wrote Astwood, "resulted in the relief of symptoms and the return to normal of the serum cholesterol and the basal metabolic rate." This medicament must for the present be used with caution.

11. The success of iodine treatment depends upon the rapidity with which an adequate dosage can reduce the enhanced oxidative processes in thyrotoxicosis.

12. Iodine is not only useful as a temporary medication in thyrotoxicosis, but is also a valuable diagnostic means. In doubtful cases it may be employed as a therapeutic test to determine the presence of thyrotoxicosis.

*Astwood, E. B.: Journal of the American Medical Association, 122, 1943.

SUCCESSFUL REMOVAL OF FOREIGN BODY WITHIN THE PERICARDIUM

Case Report

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Medical Corps, U. S. Army

A SOLDIER was admitted to a General Hospital Sept. 15, 1943, because of recurrent attacks of left shoulder and precordial pain of sufficient severity to prevent him from keeping up with his organization.

In March, 1943, he had been wounded during the battle of Fondouk Pass when a shell fragment entered the left anterior chest at the level of the third intercostal space, just lateral to the sternal border. His next recollection was twenty-four hours later when he regained consciousness in a hospital where he was told that he had been in a shocked and dazed condition. For the next few days he was troubled by a dull aching substernal pain which became sharp and quite severe with deep breathing or coughing. This complaint disappeared spontaneously. On the tenth day after hospitalization he was able to be up and about the ward and remained symptom-free until discharged to full duty with his outfit twenty-six days later. Sixteen days after leaving the hospital, while doing guard duty, he first noted a sharp pain originating in the supraclavicular region of the left shoulder and radiating down over the left chest to the region of the nipple. This pain lasted for a period of twenty-four hours and was comparable to the discomfort experienced in spraining a finger. Associated with this was a dull aching pain originating under the lower portion of the sternum and radiating out to the apex of the heart, lasting about forty-eight hours. Both pains disappeared spontaneously and no medical attention was sought. During the next two months the soldier had three recurrences of shoulder and precordial pain similar in nature and duration to the original episode and occurring during periods of rest or mild activity. Following the last attack, July 4, 1943, he was examined by a medical officer and placed on light duty. He remained in this capacity until Aug. 30, 1943, when he was referred to a General Hospital for further study and disposition because in the opinion of his medical officer he was not able to fulfill the duty requirements of a combat soldier. At that hospital he was observed during two paroxysms of chest and shoulder pain while confined to bed, and in addition it was noted that at times he had short periods of arrhythmia apparently due to runs of extrasystoles usually brought on by change of position. X-ray studies revealed a small metallic foreign body lying adjacent to the base of

Received for publication, July 21, 1944.
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the heart in the region of the right auricle and an electrocardiogram done Sept. 2, 1943, showed a low T wave in Lead 1 with normal findings in Leads 2, 3, and 4 (Fig.1). There was no complaint of dyspnea, ankle edema, or palpitation at any period. Following these examinations, the opinion was expressed that the foreign body should be removed but in another Theatre.

Physical Examination.—Examined at a General Hospital, Sept. 15, 1943, the patient was found to be a well-developed, well-nourished white man lying quietly, flat in bed, comfortable and relaxed.

Head and neck.—Head and neck were found to be normal.

Chest and lungs.—There was a small healed scar 1 by 1 cm. in diameter in the third left intercostal space adjacent to the left sternal border. The lungs were normal to percussion, palpation, and auscultation and the excursion of the thoracic cage was free and equal.

Cardiovascular.—Pulse was 84, rhythm regular, and blood pressure 108/64. Point of maximal impulse was in the fifth left intercostal space 8 cm. from the midsternal line. A grade 1 systolic murmur was heard localized over the pulmonic area and P_2 was accentuated. When the patient was made to roll to one side or sit up quickly, brief runs of extrasystoles were noted which disappeared promptly. There was no distention of the neck veins, no râles at the lung bases, no ankle edema, and the liver was not palpated.

Examination of the abdomen, genitals, extremities, and nervous system was negative.

Laboratory.—Blood count showed red blood cells, 4,600,000; hemoglobin, 14.5 Gm.; white blood cells, 6,800; polymorphonuclears 82 per cent; and lymphocytes, 18 per cent.

Urine, specific gravity was 1.020 and it was negative for presence of albumin, sugar, or significant sediment.

The sedimentation rate was 2.5 millimeters per hour (Wintrobe).

X-ray and fluoroscopic examinations, Sept. 16, 1943,* showed a metallic foreign body 8 by 6 mm. lying 8 cm. beneath the anterior skin, as marked at the time of fluoroscopy, and about 1 cm. to the right of the midline at the level of the lower border of the sixth dorsal vertebra, apparently lying close to or within the pericardial sac near the junction of the superior vena cava and the right auricle. The foreign body moved synchronously with the cardiac contraction and was not influenced by respiration. The lung fields were clear.

An electrocardiogram was made Sept. 20, 1943 (Fig. 2). T waves were inverted in Leads 1 and 4 and occasional ventricular extrasystoles were present in Lead 2. The tracing was otherwise normal. These T-wave changes as compared with the tracing made Sept. 2, 1943 (Fig. 1) at a General Hospital were interpreted as indicating myocardial damage of a progressive nature.

*Fluoroscopic and x-ray examinations done by Lieutenant Colonel C. D. Smith and Captain D. A. Russell.

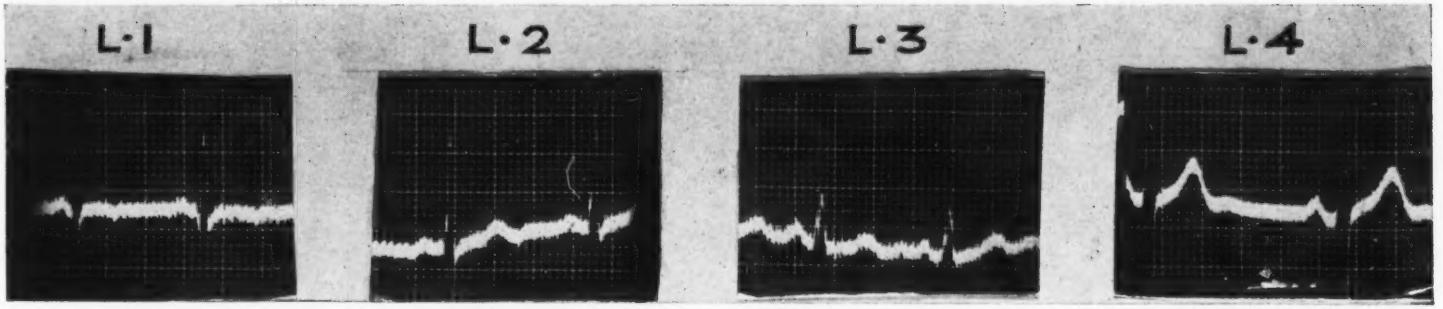

Fig. 1.—Sept. 2, 1943. Normal sinus rhythm. P-R interval 14 seconds; T_1 inverted, T_4 upright.

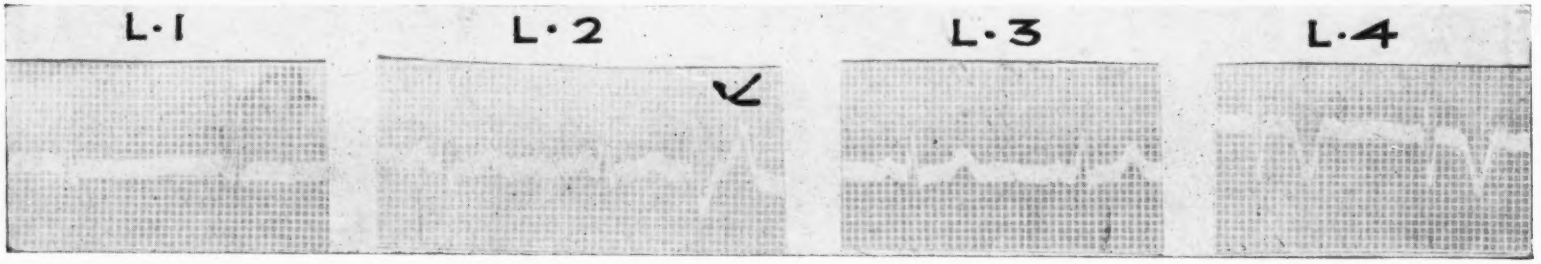

Fig. 2.—Sept. 20, 1943. Rate 70 per minute. Normal sinus rhythm. P-R interval 14 seconds; one ventricular extrasystole present in *L2*. T_1 and T_4 inverted.

In light of the evidence presented by these studies we concurred in the opinion that the foreign body should be removed. This decision was reached because there were recurrent episodes of anginal pain which were thought to arise from either the myocardium or pericardium or both, because there were extrasystoles which recurred after exercise or when changing position, because the foreign body was located in the region of the sinoauricular node where minor histologic damage might produce major physiologic dysfunction, and because electrocardiography revealed evidence of progressive myocardial damage over a relatively short period of time. Furthermore, it was necessary to give full consideration to the possibility that the foreign body might erode into the auricle or superior vena cava. Likewise, the danger of secondary infection and extensive adhesion formation at a future date confronted us.

Sept. 26, 1943, while the patient was under observation and confined strictly to bed, he developed the pain in the left shoulder and under the sternum previously described. Associated with this was a temperature elevation to 100° F., a white blood cell increase from 6,800 to 9,600 and a fall in the sedimentation rate from 2.5 to 18 mm. per hour. The electrocardiogram remained unchanged (Fig. 3) and twenty-four hours after the onset of the pain the patient felt perfectly well. The temperature returned to a normal level.

The occurrence of this episode coupled with his previous clinical course made us feel that it would be unwise to delay operation further and preparations were made to remove the foreign body at once.

The operation was performed Sept. 29, 1943, under endotracheal ether and oxygen and one-half of 1 per cent procaine solution locally infiltrated. A right parasternal incision for an extrapleural approach was made extending from the lower border of the second rib along the sternal margin to the fifth rib and the lower border of the fifth rib to the nipple line. The skin-fascia muscle flap was turned up to expose the third and fourth costal cartilages and the anterior ends of the corresponding ribs. The third and fourth costal cartilages and anterior one inch of corresponding ribs were resected subperiosteally. The posterior perichondrium and intercostal bundles were divided near the sternum and retracted to expose the internal mammary vessels which were doubly ligated proximally and distally with No. 1 chromic catgut and resected between the ligatures. The communicating intercostals were also ligated. The pleura was gently separated from intercostal bundles and posterior perichondrium and laterally from sternal border and pericardium. It was necessary to resect a portion of the sternum. The periosteum was separated anteriorly and posteriorly from the area and the bone was then removed with rongeur forceps. The pericardium was incised and the incision extended exposing the right ventricle, right auricle, and superior vena cava. There were soft adhesions between the right auricle and pericardium, right auricle and superior vena cava, and

the upper anterior portion of the right ventricle. These adhesions were separated and a foreign body approximately 1 cm. in length was found encapsulated on the anterior aspect of the right auricle in close proximity to the superior vena cava. The fragment was very gently freed and removed. The pericardium was loosely approximated with interrupted sutures of No. 1 catgut. The incision in the thoracic wall was closed approximating the intercostal bundles and posterior perichondrium with No. 0 chromic catgut, the pectoral sheath with interrupted No. 1 chronic catgut, the subcutaneous tissue with fine catgut and black silk for the skin.

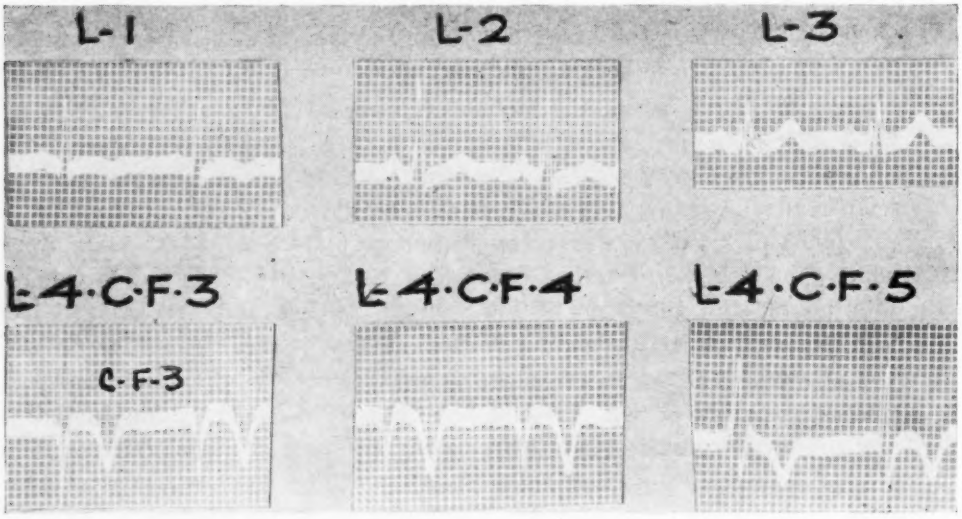

Fig. 3.—Sept. 27, 1943. Rate 80 per minute. Normal sinus rhythm. P-R interval 16 seconds; T_1 and T_4 are inverted and ST_1 is slightly convex upward. Tracing made twenty-four hours after episode characterized by chest pain, fever, leucocyte rise, and increase in sedimentation rate.

Postoperative Course.—Approximately ten hours after operation the patient complained of precordial pain and at that time a pulse irregularity was noted lasting several hours. For the first thirty-six hours there appeared a slight degree of cyanosis which was corrected by continuous oxygen therapy. For the next three days normal color was maintained by intermittent administration of oxygen. On the second postoperative day a small area of atelectasis developed in the right base posteriorly, clearing up on deep breathing, CO_2 and O_2 inhalations. On the eighth postoperative day a superficial wound infection was detected in spite of the fact that chemotherapy, which was instituted immediately after operation, had been administered in sufficient dosage to maintain a sulfadiazine blood level of 6 mg. per 100 c.c. Following adequate drainage the temperature, which had been elevated since the operation, returned to normal. On the ninth postoperative day a friction rub was noted in the right axilla unaccompanied by any discomfort or temperature elevation; this disappeared within the next forty-eight hours. On

the fourteenth day he was allowed to be up in a wheel chair and on the sixteenth day up and around the ward.

At the time of operation measures had been taken to combat disturbances of cardiac function and the following drugs placed at hand: Quinidine sulfate, 10 gr. in 100 c.c. of normal saline; calcium gluconate, 10 per cent solution for intravenous use; atropine sulfate, a 1:1000 solution of adrenalin hydrochloride and digitalis in solution for subcutaneous or intravenous administration. Happily, no evidence of rhythm disturbance or cardiac dysfunction of any character was encountered. Throughout the entire operation the pulse rate did not exceed 120 per minute, the rhythm remained regular, and the blood pressure ranged from 120 to 140 mm. of Hg systolic and from 72 to 90 mm. Hg diastolic. An electrocardiogram (Lead 2 only) (Fig. 4) was recorded at the time the foreign body was being removed from its bed and showed a normal sinoauricular rhythm and a rate of 120 per minute. Before leaving the operating room another tracing was made (Fig. 5) which showed an upright T_1, and a T wave in Lead 4 that was inverted only 1 mm. During the remainder of his postoperative course the pulse rhythm remained regular except for the brief episode mentioned in the preceding paragraph; the blood pressure remained normal. No pericardial friction rub was ever detected and repeated x-ray and fluoroscopic studies showed no evidence of pericardial or pleural fluid. Electrocardiographic tracings were taken on the first, second, and fourth postoperative days and thereafter each week until the date of discharge Nov. 16, 1943. Samples of these tracings are shown in Figs. 6, 7, and 8, indicating only slight changes in the pattern of the T waves and S-T segments, but as a whole representing no evidence of improvement over the electrocardiographic tracings made prior to operation.

In other respects the operative results have been gratifying. There has been no recurrence of the shoulder and chest pain previously experienced and no cardiac arrhythmia detected other than that noted during the first twenty-four hours after operation.

At the time of discharge from the hospital, Nov. 16, 1943, to the Zone of Interior, the patient was walking freely about the hospital and surrounding grounds without discomfort. The operative wound was healed and firm without chest deformity. Movement of the thoracic cage was free and equal and the lung fields were clear to physical examination and x-ray study. A lateral view of the chest showed a slight thickening of the right anterior pleura. The temperature was 98.2; respiration, 18 per minute; pulse, 76 per minute; rhythm regular and the blood pressure 124/72. The apex was palpated in the fifth left intercostal space 8 cm. from the midsternal line. A grade 1 systolic murmur was noted over the pulmonic area and the pulmonic second sound was accentuated. There was no evidence of distention of the neck veins or ankle edema.

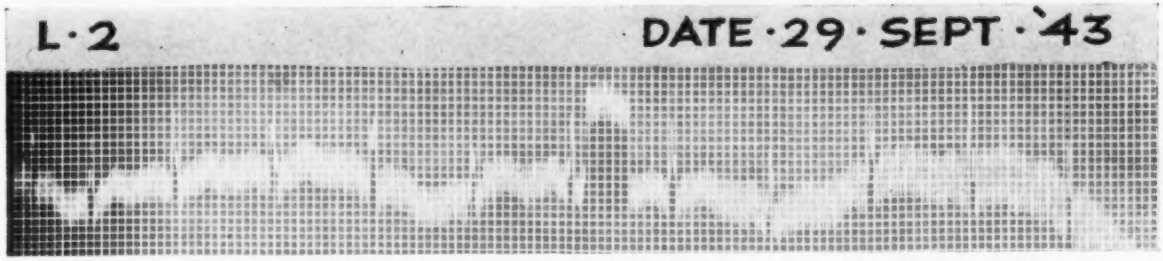

Fig. 4.—*L2* only. Rate 120 per minute. Normal sinus rhythm. Tracing made during operation.

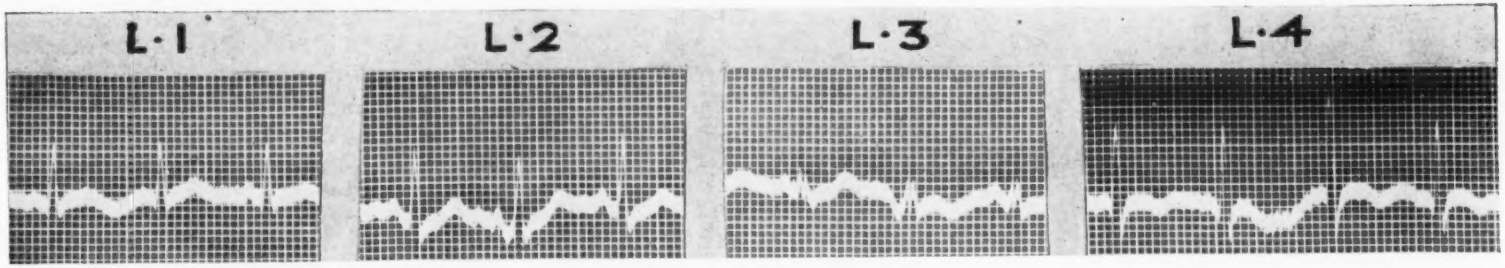

Fig. 5.—Sept. 29, 1943. Rate 110 per minute. Normal sinus rhythm. P-R interval 12 seconds; T_1 upright, T_4 inverted 1 mm. Tracing made immediately after operation.

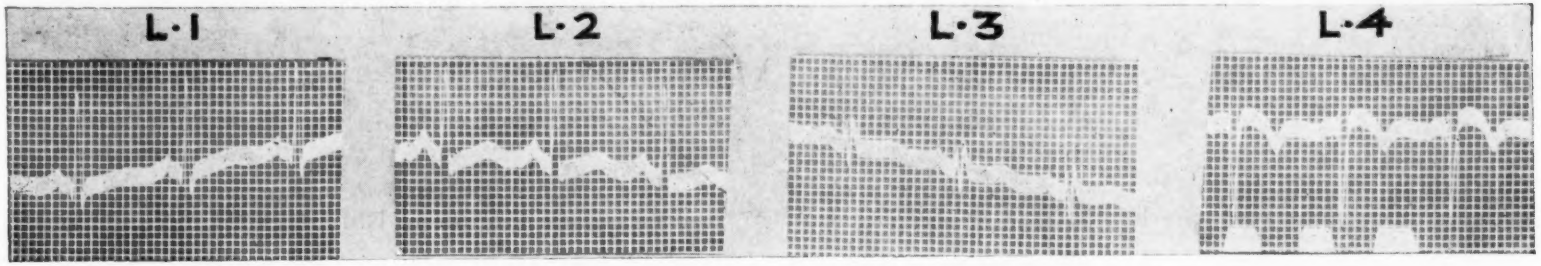

Fig. 6.—Oct. 6, 1943. Rate 110 per minute. Normal sinus rhythm. P-R interval 14 seconds; R4 low; T_1 low but upright, T_7 inverted.

Fig. 7.—Oct. 11, 1943. Rate 90 per minute. Normal sinus rhythm. P-R interval 12 seconds; R4 low; T1 and T4 are inverted.

Fig. 8.—Nov. 15, 1943. Rate 80 per minute. Normal sinus rhythm. P-R interval 14 seconds; T_1 and T_4 inverted.

An electrocardiogram (Fig. 8) still showed inverted T waves in leads 1 and 4, with a normal sinus rhythm. The sedimentation rate was now 2.5 mm. per hour and blood and urine studies were normal.

SUMMARY

1. A case is reported of the successful removal of a metallic foreign body from the vicinity of the sinoauricular node producing adhesions between the anterior wall of the right auricle, superior vena cava, and pericardium, and extending downward over the right coronary sulcus onto the anterior wall of the right ventricle.

2. At the time of our first examination myocardial damage was present as indicated by recurrent attacks of precordial pain, cardiac arrhythmia, and inversion of the T waves in Leads 1 and 4 of the electrocardiogram.

3. There was no recurrence of the precordial pain and no further disturbance of rhythm was noted after the first postoperative day, in the period of seven weeks' postoperative observation.

4. No essential change was noted in the electrocardiographic tracings taken before and after operation.

The authors wish to express their gratitude to Lieutenant Colonel John P. Williams for his advice in the management of this case and to Captain George B. Craddock for the administration of the anesthetic.

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BONE REGENERATION FOLLOWING OSTEOMYELITIS

LAURENCE H. MAYERS, M.D., CHICAGO, ILL.

THE processes of bone destruction and bone restoration in an osteomyelitis of the phalanges of a finger go on almost simultaneously. Nature's effort at restoration may seem to be delayed and its work is not instantly observable, but study of cellular destruction and restoration shows that they work harmoniously. Indeed, while the osteoclasts, regarded as destroying cells, are at work, they are preparing for the constructing cells, the osteoblasts, into which they change themselves when the time comes.

McLean and Bloom, for instance, observed that, "recovery (from bone necrosis) occurred by extensive intramembranous formation of new bone, accompanied by development of large numbers of active osteoblasts from the fibroblasts of the scar. These observations throw new light on the pathogenesis of experimental osteitis fibrosa which appears to develop, in part at least, as a reaction to the death or injury of the cellular elements of bone. Of more general biologic interest is the evidence that osteoblasts are not permanently differentiated cells, for they have been seen to change into phagocytes, osteoblasts, and fibroblasts; further fibroblasts have been seen to develop into osteoblasts which are then associated with the formation of new bone."

"The question," say Baetjer and Waters, "will present itself as to why in one case there is bone destruction and in the other bone production. The point of contact between the lesion and the bone is the point of stimulation. It takes nature some little time to lay down bone, so if the infection or lesion is virulent, the point of contact is swept away and a new one formed before there has been time for new bone formation; hence the process is entirely destructive. On the other hand, if the point of contact remains stationary for a short period, then nature has time to lay down new bone. So there are two well-defined changes taking place in bone, namely, destruction, indicating an advancing lesion, and production, indicating a lesion that is retrograding and is probably under control."

Wilensky says, "in bones, the seat of an osteomyelitic process, repair of the osseous tissue goes hand in hand with bone destruction," and Holman refers to the "almost infinite power of repair in bone, especially in infancy and early youth."

And, finally, Wilensky: "It is probable that all cells are formed into osteoblasts and can become osteoclasts. Just as osteoclasts originate from osteoblasts and their derivatives, they can again become osteoblasts and bone cells after their osteoclastic activity is over."

Received for publication, Sept. 11, 1944.

The foregoing statements are authoritative, theoretical, and perhaps observational descriptions in their application to the course of the osteomyelitis in the case under discussion. They are to be read in connection with the examination of the x-ray films, which tell as far as pictures can, the story of both the destructive and the restorative processes.

The patient in this case was a policeman who was bitten on the middle finger of his left hand by a man whom he was arresting. Striking another person on the teeth by accident would seem to be less risky than a deliberate bite, but even such accidental contacts are not an infrequent

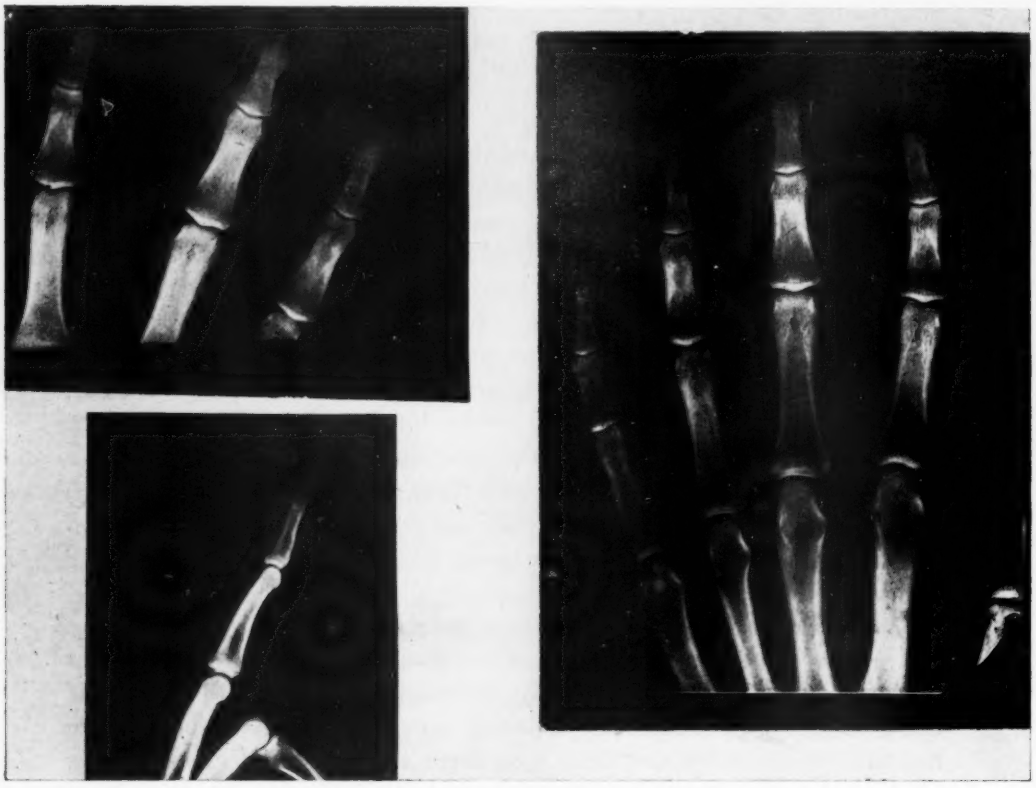

Fig. 1.—Sept. 5, 1938. This first roentgenogram was taken to determine whether a fracture resulted from a human bite near the end of the middle finger of the left hand. A human bite may develop a pressure as high as 300 pounds to the square inch. The finger was lacerated, red, sore, and swollen. No fractures were disclosed. Incision below the nail brought forth a copious, purulent discharge. Drainage was deemed adequate.

Sept. 9, 1938, four days later, it was thought that the infection was localized to the terminal phalanx. However, mouth organisms were numerous and virulent.

source of infection, and there have been cases in which a mixed anaerobic infection from organisms of the mouth resulted. The latter was true in this case. Pyogenic organisms, spirilla, and anaerobes were all present as the case progressed.

It is also to be noted that the patient in this case was 40 years of age, far beyond the age at which bone restoration is regarded as assured. Considering the extent of the destruction, the very marked soft tissue

involvement, and also the virulence of the infection, the bone restoration is the more interesting. And, finally, both the regenerative and the destructive processes are rather completely illustrated. Figs. 1 to 8 cover the entire period. Too often such a series is impossible because amputation offers an easier and speedier way to recovery.

A finger more or less is taken as a matter of consequence or inconsequence by the patient according to his occupation and economic condition. To a worker with pick and shovel such a loss might seem compartively unimportant; to a piano virtuoso it would be vital. The patient in this case refused to permit the amputation, and so we have the x-ray films.

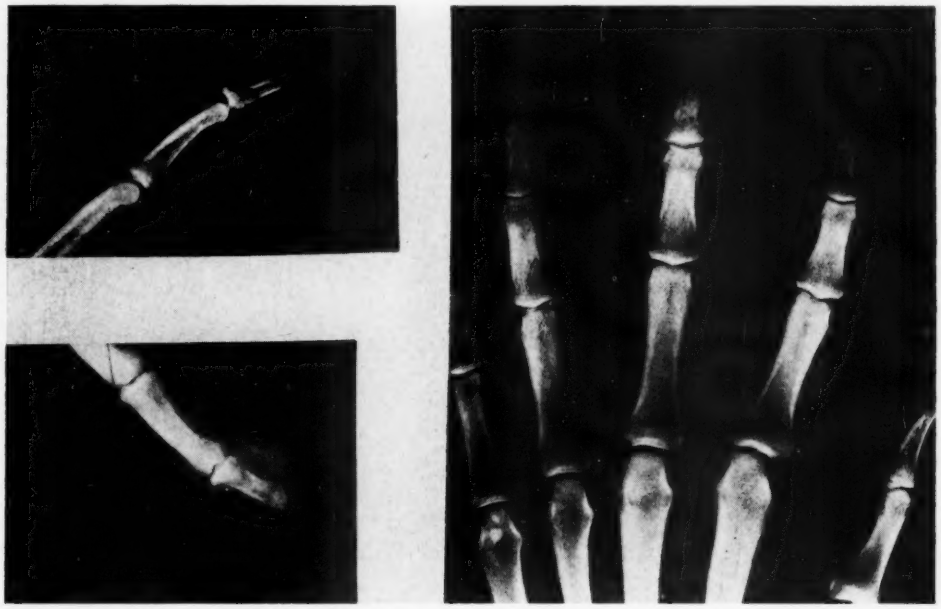

Fig. 2.—Sept. 16, 1938, six days later, while drainage was satisfactory, there developed a sloughing and necrosis around the nail. The nail was removed. Five days later osteomyelitis of the terminal phalanx was apparent. The destructive process was rapid. In the course of this infection, laboratory examination revealed staphylococci, spirilla, and anaerobes.

Beyond these, and for more particular information, reference is made to Knavel's text[13] and to Auchincloss' chapter in *Nelson's Loose Leaf Surgery*.[2]

In dealing with any infection of the hand it is, of course, of first importance to have a thorough knowledge and understanding of the detailed anatomy of that very useful member. No part of the body, except the mental organ and the eye, is so much used or is so useful. The anatomy of the hand is complex and invites and deserves extended study. In the matter of hand infections, understanding of the principles of free drainage is particularly stressed by Kanavel. Auchincloss says that "early adequate drainage means early, comfortable convalescence. Delay means more necrosis, more dressings, osteomyelitis, in-

fection of the joint, and, if the lesion be near the distal flexion crease, a threatened tendon sheath."

The policeman was admitted to the hospital the morning after the wound was received. The following day the finger was incised below the nail, liberating a quantity of foul, purulent material. Drainage continued to be rather profuse for some time. The destructive process was advancing, as Figs. 1 to 7 show. Twelve days after the patient was admitted to the hospital the roentgenologist's report showed almost complete dissolution of the middle portion of the phalanx and tip with moderately advanced invasion of the distal three-fourths of the middle phalanx, and involving the distal joint; the soft tissues still showed considerable thickening.

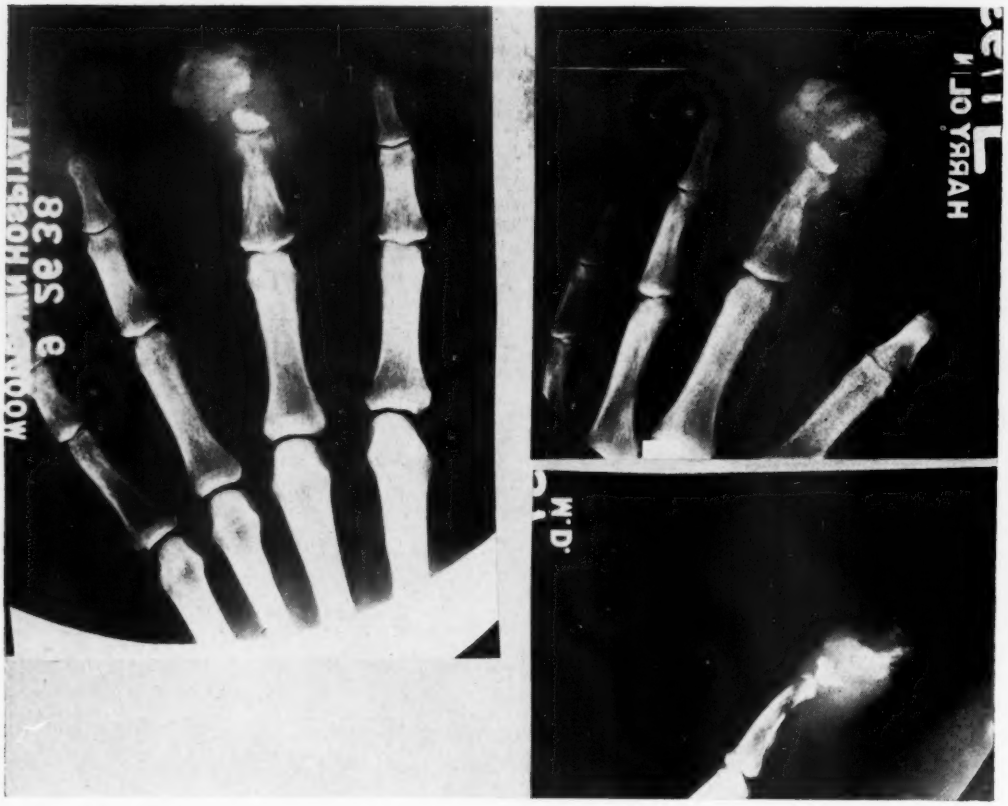

Fig. 3.—Sept. 26, 1938, ten days later, the picture disclosed almost complete dissolution of the middle portion of the phalanx and tip, with moderately advanced invasion of the distal three-fourths of the middle phalanx. Subluxation of the terminal joint was practically complete. Sequestration of bone fragments was under way. The destructive process was receding in the usual way. The sequestration indicated the first effort at restoration of the destroyed bone.

Thus, it appears that the infection was advancing according to rule—from the distal anterior closed space by way of the nutrient foramen into the medullary cavity, with an osteomyelitis as the result. Thence the spread is to the flexor subtendinous space of the base of the distal phalanx and into the joint cavity, and so on to the middle phalanx with

probably entry to the tendon sheath. In the case under discussion there was involvement of (1) soft tissue, (2) bone, (3) joint, and (4) tendon.

The outcome of such a destructive and progressive osteomyelitis will depend on a number of things—the type of the organisms present, the age and condition of the patient, and, probably most important of all, the treatment.

The mixed infection, particularly one including anaerobes, is more serious than one involving a single organism. A child has a better chance to combat the infection and to obtain bone regeneration than an older person. The results in the case of the policeman, however, indicate that his age did not work against him. His recuperative power is one of the factors that give the case a lively interest.

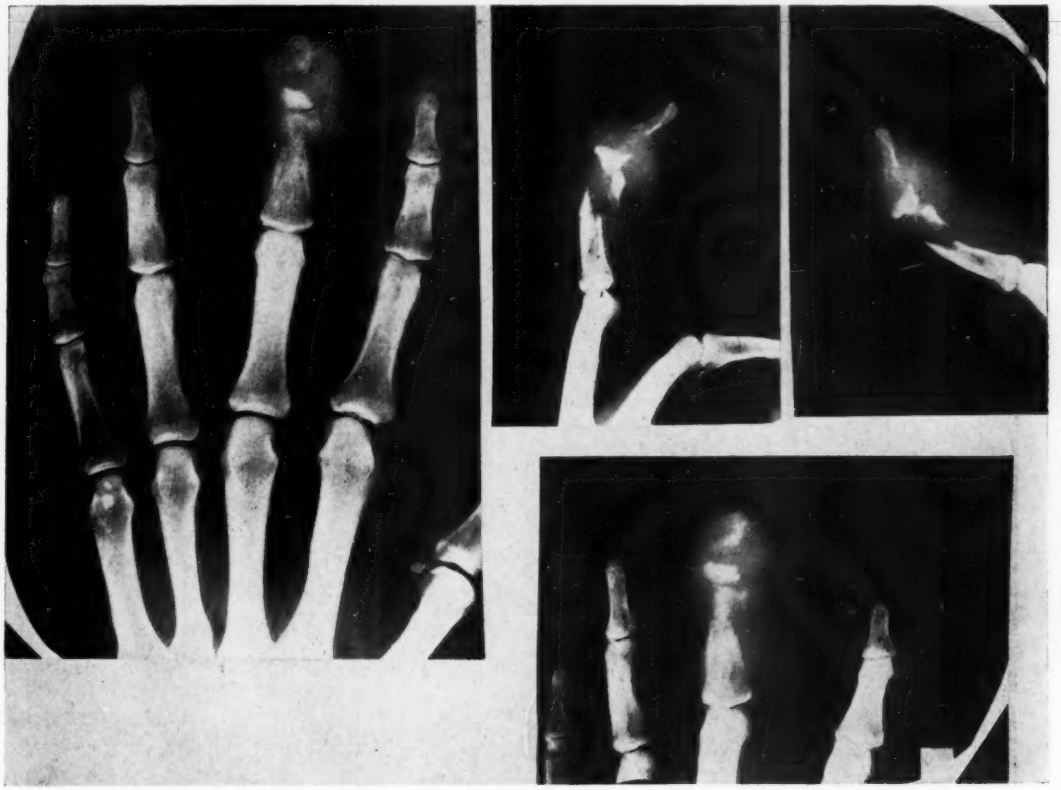

Fig. 4.—Sept. 30, 1938, there was further invasion toward middle joint and increasing destruction of distal phalangeal bone. Sequestrated fragments of bone were visible as evidence of the conflict between living and dead cells. Hot applications were discontinued.

The treatment covered the conventional range, and the conventional range is wide. The technique may change, but the principles are constant. Heat and cold, dryness and moisture, elevation and dependency, rest and activity, protection and massage, darkness and light, asepsis and germicides, pressure and its avoidance are all listed by Auchincloss, and "play their parts, and a host of other things besides."

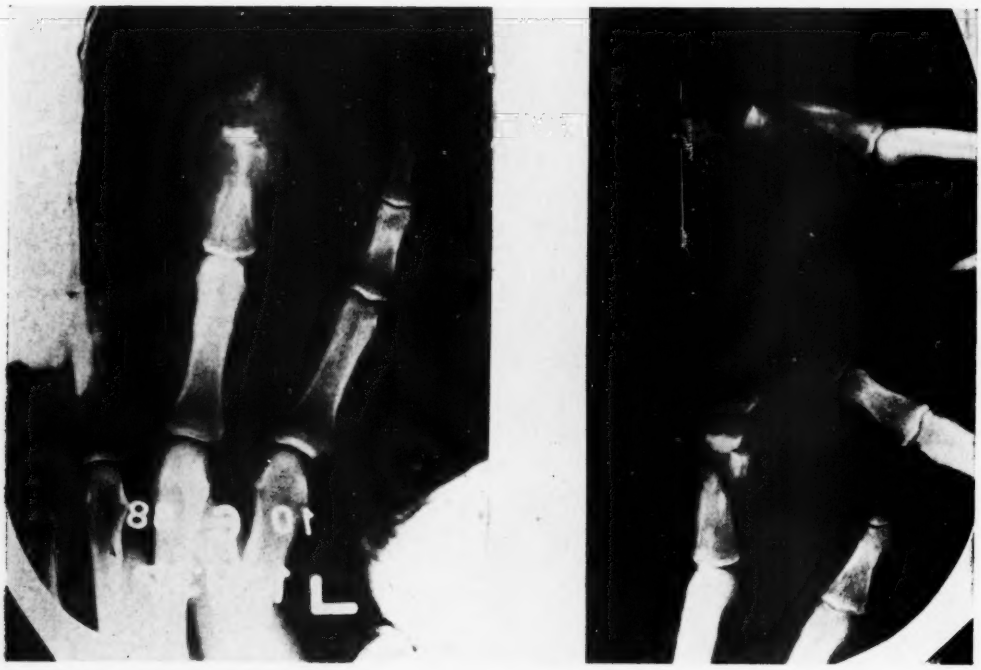

Fig. 5.—Oct. 6, 1938, the osteomyelitis was progressing and the flexor tendons were undoubtedly involved. Edema was subsiding.

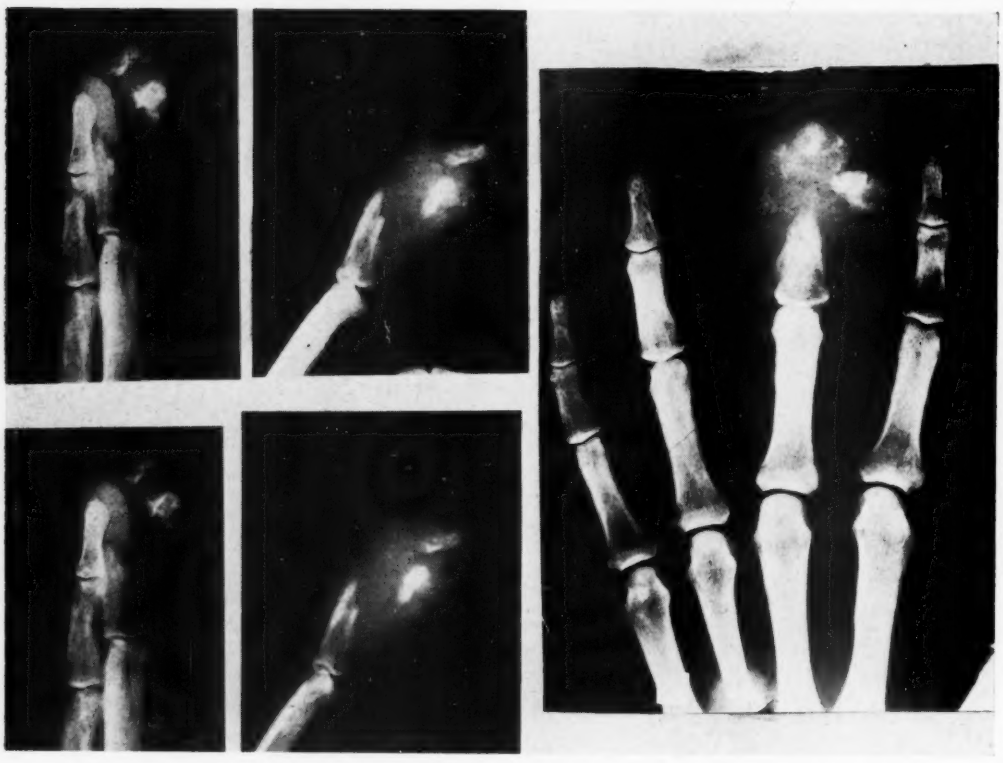

Fig. 6.—Oct. 10, 1938. Loose fragments of bone belonging to the distal phalanx marked the sequestration of the dead from the living cells. The sequestration level was the boundary line between the living and the dead cells and the point of conflict between them. If drainage is not complete, the living cells will be poisoned and die. In that case the work must be begun again at another joint by a new army of phagocytes, aided by a new incision for drainage. Note the extension into the middle phalanx.

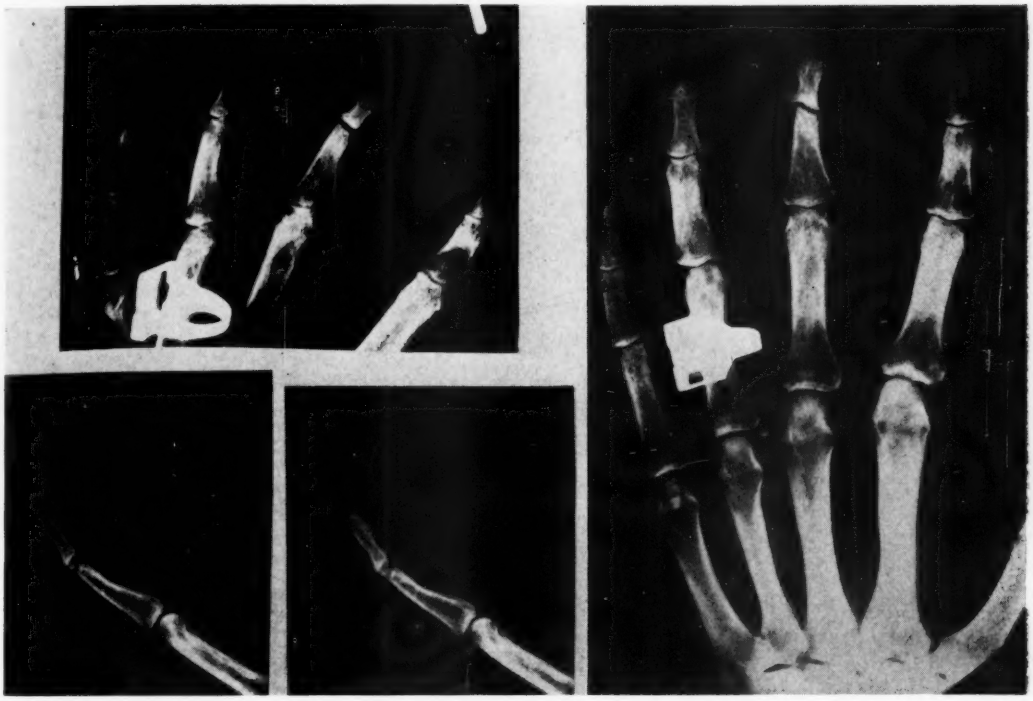

Fig. 7.—Nov. 9, 1938. While the middle and proximal phalanges showed further invasion and the periosteum was stripped in the middle portion, there was visible improvement of the bone of the distal phalanx. At that point sequestration was completed and the bone was reorganizing its normal contour.

Fig. 8.—Nov. 16, 1938. This picture was taken after the hand had completely healed.

The final purpose of all treatment was to give the phagocytic type of cell a chance to work to the maximum advantage. All that promotes this, according to Auchincloss, is good; whatever hinders is bad. Indeed, if the welfare of the living cells, hard at work at the sequestration lines, be carefully attended to, much that was considered dead at one time would seem to be used in various ways as framework or even material with which the living cells reconstruct the part.

"Drainage," he says, "is perhaps the most subtle and important. Until sufficient time has elapsed for the sequestration bit of bone to be wholly separated through the action of living phagocytes, from the bone that yet lives—drainage plays a part."

If the drainage is not effective for any reason and the irritating discharges are blocked, they are thrown back on the living cells at work which are thus poisoned and die. The work of sequestrating dead bone from living bone must then be carried on by a new army of cells farther along the bone, after another incision.

In the case under discussion, the drainage first established may have been imperfect, or the infection may have been particularly virulent, probably the latter. The destruction went on past the middle joint and into the middle phalanx, the distal joint was involved and the tendon sheath as well.

Five weeks after the wound was received, the finger was reoperated upon. Incision was made over the radial side from the midportion of the terminal phalanx to the mid-portion of the proximal phalanx. A small amount of necrotic tissue was removed. The flexor tendon was exposed and found to be destroyed distal to the proximal and middle phalanx. A posterior splint was applied.

As the authorities heretofore quoted have stated, it takes nature some time to lay down bone. The struggle of the living cells, however much help they may receive from the treatment, is not short and it is always desperate. In this case it seems that all the good as well as the bad factors were present and working. But it was four months after the removal of the tendon before the roentgenologist reported that much of the bone atrophy had disappeared. The osteomyelitic process had thoroughly abated and the cortex was commencing to appear. The terminal joint, of course, was partially ankylosed.

The x-ray films permit one to trace the course of a virulent infection resulting in a destructive and progressive osteomyelitis, from the beginning to the final climax of bone restoration. The comment and citations will doubtless be helpful in pointing the way to more extended study. The policeman patient has a good usable finger.

This report was made possible through the courtesy of Dr. R. K. Packard, of the staff of the Woodlawn Hospital of Chicago. Dr. Packard was in charge of the case and was in continuous attendance from the beginning and performed the operation.

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A PRACTICAL CONVERSION OF FLAGG TYPE LARYNGOSCOPES

RODGER E. MACQUIGG, M.D., NEW YORK, N. Y.
(From the Department of Research Surgery, Ohio State University)

INTRATRACHEAL anesthesia, properly applied, offers such rewards in safety and convenience, particularly in operations about the head and in chest surgery, that it should be in use in all hospitals. Moreover, there are emergencies which call for the accurate aspiration of inhaled vomitus, or occasionally for the removal of foreign bodies above the level of the glottis, in which delay while a specialist is being sought might prove serious. Those who have seen the dramatic relief afforded by tracheal aspiration to patients who are too weak to raise the secretions that are suffocating them, and likewise those who are aware of how frequently the battle is lost because of that most subtle of killers, chronic anoxia, will avail themselves as far as possible of the positive and simple direct-vision technique of laryngoscopy.

The purpose of this communication is to call attention to some points of practical importance to those undertaking laryngoscopy as it assumes its rightful place in general medical and surgical practice. The first point is of the greatest importance—to emphasize that the neck of the patient should be strongly flexed on the chest and relaxed instead of being extended as the beginner usually assumes. The head itself may then be extended (bent backward) upon the neck at the atlanto-occipital level as much as is possible with the neck thus flexed upon the chest.

There is usually no difficulty in passing the laryngoscope blade to raise the back of the tongue (as the patient lies supine with head toward operator) and in exposing the epiglottis, although the overly anxious may fail to get oriented squarely by hurrying over the landmarks. The blade is then withdrawn slightly to scoop under the tip of the epiglottis and lift it forward. If the laryngoscope is entered too far it overrides the slanting glottis and enters the esophagus, yet if it is withdrawn too far the tip of the epiglottis is released and flips back down over the glottis. Lateral deviation gives entry to the pyriform fossae, which may be mistaken for the glottic chink. All this, plus the necessity for firm and constant lifting, may make control difficult. The laryngologist, using the beautifully balanced Jackson instrument, has minimal difficulty because his instrument is C shaped and he uses the horizontal handle bar not only to lift directly but as a lever to control deviation.

However, there is a definite place for the self-contained laryngoscope. Flagg[1] recognized that, for intubation and for emergency work, a laryngoscope was needed with a large lumen, open along one side to permit ready disengagement of tubes or instruments, and that it should be

Aided by a grant from the Comly Fund for Research.
Received for publication, Sept. 26, 1944.

self-contained, ready for instant use and control. He eliminated the dangling cords and battery box by placing flashlight batteries within the handle, developing the pattern now so widely used under his name. Difficulty is noted, particularly by the novice, because of the lack of a horizontal member for the handle bar. This forces the hand to apply a twisting stress to the vertical handle, and even with a strong wrist there results marked loss of delicacy of control. There is also a common tendency to *pry,* using the upper teeth as a fulcrum, which may cause pain or damage even though an attempt is made to provide a shield for the teeth. It must be realized that particularly in intubation and in individuals with thick short necks, considerable force must be applied to the tissues behind the hyoid bone to obtain adequate exposure, sometimes enough to lift the patient's head from the table. If done correctly there is no danger of local trauma as the parts shift together to the required alignment. The point is that the load lies largely on the tip of the blade.

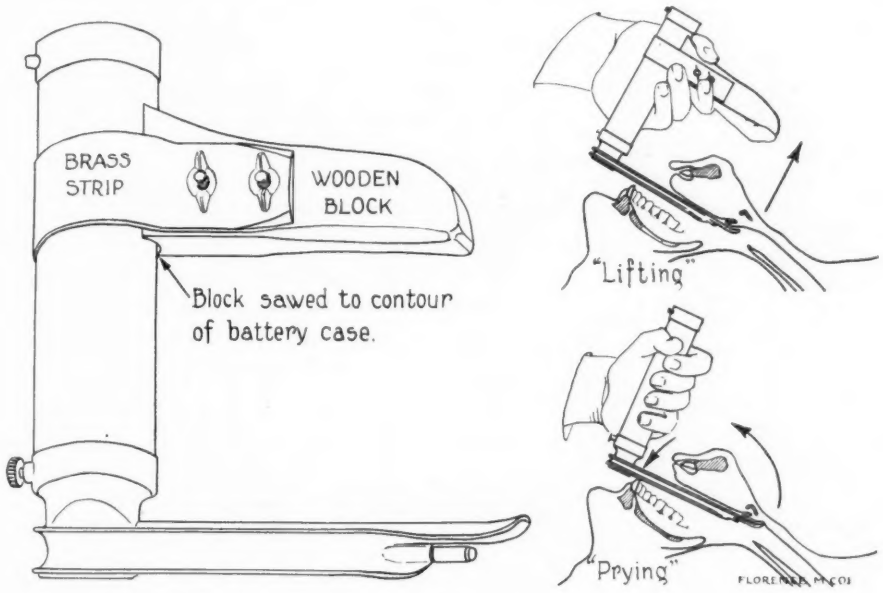

Fig. 1.—Flagg pattern laryngoscope, showing proper use *to lift* rather than to pry.

An adjustable wooden handle was therefore added to the usual Flagg laryngoscope used for intubation. (See Fig. 1.) In thoracic operations performed during the past year at the University Hospital, members of the cooperating research surgery and anesthesia departments found their work greatly facilitated by this simple addition. Since then I have seen the excellent laryngoscope developed by Dr. U. H. Eversole, in use at the Lahey Clinic. This is operated by small batteries in the handle but is much nearer in proportions to the Jackson type than are the Flagg models. It is C shaped (provided with a horizontal member

for the handle). Although it is not described in the literature it is available commercially. It is felt that this note is warranted, however, by the number of Flagg type laryngoscopes already distributed whose usefulness could be readily increased by adding such a handle to facilitate their proper use. It is of interest to note that in some modifications of the basic Flagg design the vertical handle has been angled toward the blade in an attempt to secure this more favorable leverage and control.

MacIntosh[2] has recently described a model which has an upcurved blade, to be passed to the base of the tongue and to lift from this point without engaging the epiglottis, but after brief trial I find the merits of this clever simplification of the technique open to question. Wiggin proposes still another modification of the blade for intubation by flaring the side. The appearance of these reports suggests the further room for improvements in the basic Flagg design, but in some form his valuable contribution should be used more extensively. The full techniques are ably discussed in the readable and authoritative books by the Jacksons,[4] and Flagg.[5]

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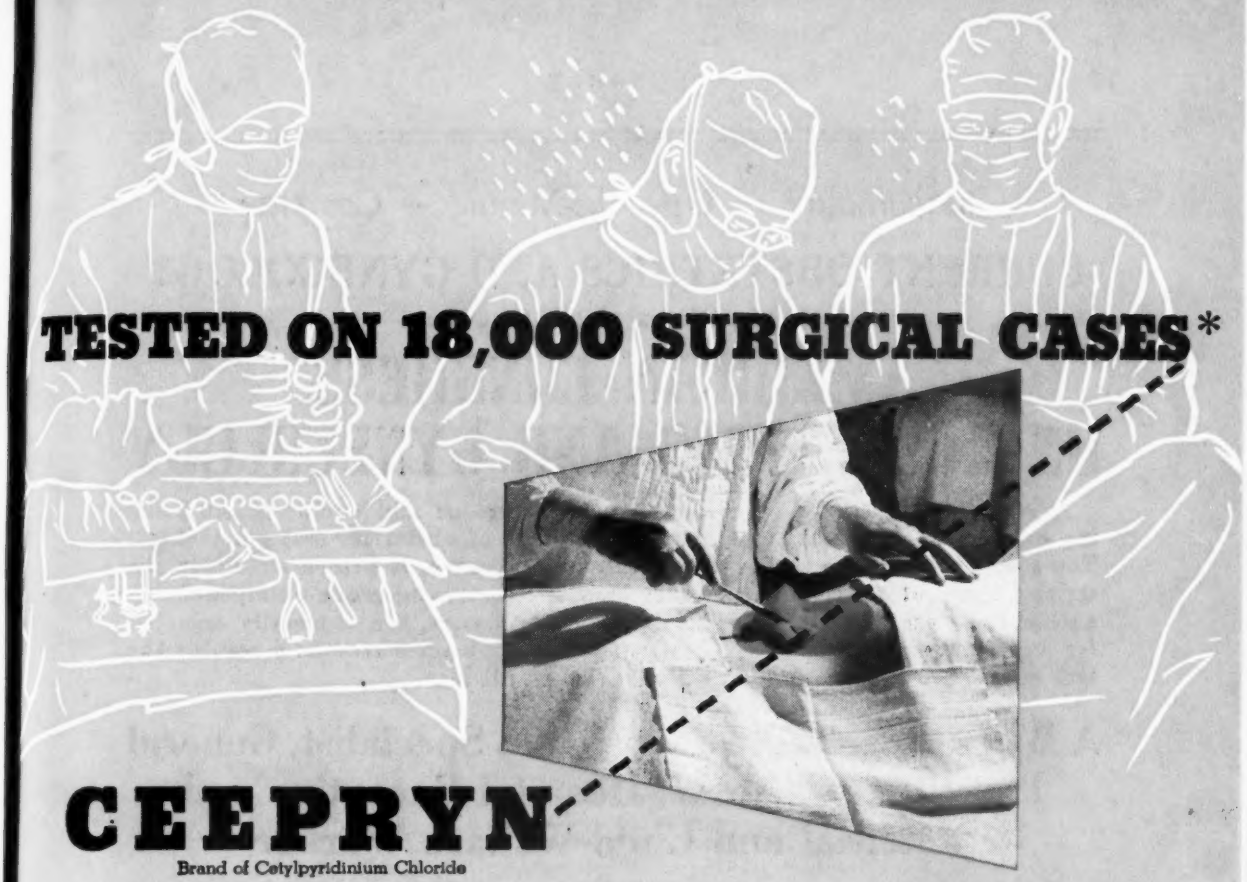

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